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L7 ANSWER 1 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
2001:400089 Document No.: PREV200100400089. Clinical relevance of the **minor histocompatibility antigen HA-1** in allogeneic bone marrow transplantation between HLA identical siblings. Tait, B. D. (1); Maddison, R.; McCluskey, J.; Deayton, S.; Heatley, S.; Lester, S.; Bardy, P.; Szer, J.; Grigg, A.; Spencer, A.; Schwarer, A.; Holdsworth, R.. (1) Victorian Transplant and Immuno Service,
Rothey Bone Marrow Research Center, Royal Melbourne Hospital, 2nd Floor,

Info.: XVIII International Congress of the Transplantation Society Rome, Italy August 29-September 01, 2000 Transplantation Society. ISSN: 0041-1345. Language: English. Summary Language: English.

L7 ANSWER 2 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
2001:249479 Document No.: PREV200100249479. **HA-1** **minor histocompatibility antigen** disparity and AGVH disease after bone marrow transplantation in thalassemia. Nesci, S. (1); Buffi, O. (1); Iliescu, A. (1); Andreani, M. (1); Lucarelli, G. (1). (1) Divisione di Ematologia, Centro Trapianto di Midollo Osseo-Ospedale di Muraglia, Pesaro Italy. European Journal of Immunogenetics, (April, 2001) Vol. 28, No. 2, pp. 271. print. Meeting Info.: 15th European Histocompatibility Conference Granada, Spain March 27-30, 2001 ISSN: 0960-7420. Language: English. Summary Language: English.

L7 ANSWER 3 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
2001:238451 Document No.: PREV200100238451. Detection and quantification of **minor histocompatibility antigen**-specific T-cells by flow cytometry and 5' nuclease assay. Eiz-Vesper, B. (1); Slateva, K. (1); Fuchs, N. (1); Blasczyk, R. (1). (1) Department of Transfusion Medicine, Hannover Medical School, Hannover Germany. European Journal of Immunogenetics, (April, 2001) Vol. 28, No. 2, pp. 235. print. Meeting Info.: 15th European Histocompatibility Conference Granada, Spain March 27-30, 2001 ISSN: 0960-7420. Language: English. Summary Language: English.

L7 ANSWER 4 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
2001:49768 Document No.: PREV200100049768. Genomic organization of the **human** cholesterol-responsive ABC transporter ABCA7: Tandem linkage with the **minor histocompatibility antigen** **HA-1** gene. Kaminski, Wolfgang E.; Piehler, Armin; Schmitz, Gerd (1). (1) Institute for Clinical Chemistry and Laboratory Medicine, University of Regensburg, Franz-Josef-Strauss-Allee 11, D-93042, Regensburg: gerd.schmitz@klinik.uni-regensburg.de Germany. Biochemical and Biophysical Research Communications, (November 30, 2000) Vol. 278, No. 3, pp. 782-789. print. ISSN: 0006-291X. Language: English. Summary Language: English.

AB We have recently cloned a novel cholesterol-responsive ABC transporter, designated ABCA7, which is predominantly expressed in **human** leukocytes. Here we report the structure of the **human** ABCA7 gene. The ABCA7 gene spans a region of apprx32 kb and comprises 46 exons. Its putative promoter sequence contains potential binding sites for transcription factors with roles in hematopoiesis and cholesterol metabolism. Surprisingly, sequence analysis of the ABCA7 3' gene flanking region revealed that the terminal exon of ABCA7 borders immediately on the 5' end of the coding region of the recently identified **human** **minor histocompatibility antigen HA-1**. We demonstrate that the coding regions of ABCA7 and **HA-1** are physically separated by a 1.7-kb intergene region. Subsequent genomic structure analysis showed that the **HA-1** gene consists of 23 exons which extend across a 16-kb genomic region. Our results provide evidence that the genes for the **human** **minor histocompatibility antigen HA-1** and the ABC transporter ABCA7 are arranged in a head-to-tail array and that both genes localize to a common locus of apprx48 kb size on chromosome 19p13.3.

specific **minor histocompatibility antigen** (mHag) **HA-1** and HA-2 specific CD8+ T cells associated with complete molecular remission after donor lymphocyte infusion (DLI) for relapsed CML. Marijt, W. A. F. (1); Kester, M. G. D. (1); Goulmy, E. (1); Mutis, T. (1); Drijfhout, J. W. (1); Willemze, R. (1); Falkenburg, J.
H. F. (1). (1) Depts of Hematology and Immunohematology, Leiden University
Medical Center, Leiden Netherlands. Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 478a. print. Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology. ISSN: 0006-4971. Language: English. Summary Language: English.

AB DLI results in complete remission (CR) of relapsed CML after allogeneic (allo) SCT in 70-80% of the cases. To evaluate the hematopoiesis-specific mHag **HA-1** and HA-2 as possible target antigens involved in this anti-leukemic effect, we studied the kinetics of anti-**HA-1** and -HA-2 CD8+ T cells during the clinical response to DLI in an HLA-genotypically identical female donor-recipient pair. Normal patient hematopoietic and leukemic cells expressed both **HA-1** and HA-2 whereas donor cells were negative for these polymorphic antigens. PBL were isolated from the patient before and weekly after a single low dose of DLI for a hematological relapse of CML after T cell-depleted allo SCT. The cells were stained with PE-labeled HLA-A2/**HA-1**, -HA-2 or -HY tetramers, and counter-stained with FITC- or Cy5-labeled anti-CD3, CD8, or HLA-DR antibodies. After SCT but prior to DLI only very low numbers of anti-**HA-1**, -HA-2, or -HY T cells were found in peripheral blood (15/ml). From 5 weeks after DLI a 160-fold increase of anti-HA-2 CD8+ T cells, and an 80-fold increase of anti-**HA-1** CD8+ T cells was observed which was followed by a transient pancytopenia. No increase in anti-HY T cells was observed. HA-2 specific CD8+ T cells were 51/ml (week (wk) 3), 1175/ml (wk 5), 2509/ml (wk 6), 1720/ml (wk 7), 201/ml (wk 8), 167/ml (wk 9), 130/ml (wk 10) and varied between 26/ml and 110/ml from wk 11 until wk 26. **HA-1** specific CD8+ T cells were 34/ml (wk 3), 82/ml (wk 5), 195/ml (wk 6), 1265/ml (wk 7), 151/ml (wk 8), 183/ml (wk 9), 223/ml (wk 10), and slowly decreased from 272/ml at wk 11 to 27/ml at wk 26. The decrease in **HA-1** and HA-2 specific CD8+ T cell count was associated with conversion from mainly patient hematopoiesis to full donor chimerism. All anti-**HA-1** and -HA-2 CD8+ T cells were activated as illustrated by co-expression of HLA-DR. The patient developed transient grade I GVHD of the skin requiring no systemic treatment, and 12 weeks after DLI she entered a molecular CR as measured with RT-PCR using BCR/ABL specific primers. In conclusion, using **HA-1** and HA-2/HLA-A2 specific tetramers we demonstrated a profound increase in CD8+ T cells specific for the hematopoiesis associated **HA-1** and HA-2 mHag coinciding with transient pancytopenia, conversion to full donor chimerism and complete disappearance of BCR/ABL, resulting in an ongoing molecular CR of a relapsed CML after alloSCT.

L7 ANSWER 6 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
2001:54933 Document No.: PREV200100054933. Rapid identification of **minor histocompatibility antigen HA-1** subtypes H and R using fluorescence-labeled oligonucleotides.
Kreiter, S.; Wehler, T.; Landt, O.; Huber, C.; Derigs, H.-G.; Hess, G. (1). (1) III. Medical Department of Medicine, Hematology, Oncology and Pneumology, Johannes Gutenberg-University, Langenbeckstr. 1, 55131, Mainz:

English. Summary Language: English.

AB Donor-recipient disparity of the **minor histocompatibility antigen HA-1** is relevant for the development of graft-versus-host disease after HLA-matched sibling allogeneic bone marrow transplantation in HLA-A*0201-positive individuals. Two different alleles of **HA-1** with a single amino acid polymorphism have been identified. Here we describe a time- and cost-efficient method for **HA-1** typing of genomic DNA, using site-specific hybridization probes with the LightCycler. This method was compared with standard techniques as sequencing or allele-specific polymerase chain reaction (PCR) and proved to be specific, reliable and reproducible. We conclude that **HA-1**-subtyping using fluorescent-labeled oligonucleotides represents a attractive method for the screening of samples before allogeneic transplantation in HLA-A*0201-positive individuals.

L7 ANSWER 7 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS

2001:317075 Document No.: PREV200100317075. The genetic factors which affect the outcome of unrelated bone marrow transplantation. Madrigal, J. Alejandro (1); Shaw, Bronwen E. (1); Brookes, Paul; Potter, Mike; Prentice, H. Grant; Goldman, John M.; Little, Ann-Margaret (1); Travers, Paul J. (1); Pay, Andrea L. (1). (1) Anthony Nolan Research Institute, Royal Free Hospital and UCL School of Medicine, London UK. Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 417a. print. Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology. ISSN: 0006-4971. Language: English. Summary Language: English.

AB The genetic differences between recipients of bone marrow transplants and their unrelated donors that contribute to the outcome of the transplant remain largely undefined. Until recently, the only loci considered relevant for matching have been the histocompatibility loci, HLA-A, B and DR, and even here analysis of the consequence of disparities in these loci has been complicated by the use of low to medium resolution HLA typing methods. We have studied 139 unrelated bone marrow transplants, typing for all six major HLA loci at the highest molecular resolution. We have found examples of mismatches at all loci tested in individuals previously considered to be matched. The cohort who are matched for HLA loci at the molecular level can be used to identify the influence of mismatches at non-HLA loci on survival and the graft versus host response. We have studied other loci both within and outside the MHC that may contribute to post transplant complications, including the MICA genes, NK receptors and the dimorphic **minor histocompatibility antigen HA-1**. From the results we have obtained on the effect of matching at the histocompatibility loci it appears, as expected, that matching for both class I and class II loci is associated with good survival (82%), while mismatches at either class I or class II loci, or mismatches at both a class I and class II locus, are associated with poorer survival (45% versus 30%). An HLA-DPB 1 mismatch alone can be detrimental to survival (82% versus 55%). We have analysed the influence of histocompatibility gene mismatches on GvHD, both acute and chronic, and to date have found the only association to be between class I locus mismatches and acute GvHD; we have found no associations with chronic GvHD. Results were found to be independent of T cell depletion of the graft. A MICA mismatch does not appear to affect outcome and **HA-1** incompatibility in HLA-A*0201 positive patients does not affect survival (50% matched versus 45% mismatched) or GvHD susceptibility.

L7 ANSWER 8 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS

graft-versus-host disease after HLA-identical sibling bone marrow transplantation in Japanese patients. Murata, Makoto; Emi, Nobuhiko (1); Hirabayashi, Noriyuki; Hamaguchi, Motohiro; Goto, Seiichi; Wakita, Atushi; Tanimoto, Mitsune; Saito, Hidehiko; Kodera, Yoshihisa; Morishita, Yoshihisa. (1) First Department of Internal Medicine, Nagoya University School of Medicine, 65 Tsurumai, Showa, Nagoya, 466-8560: s1nai@med.nagoya-u.ac.jp Japan. International Journal of Hematology, (October, 2000) Vol. 72, No. 3, pp. 371-375. print. ISSN: 0925-5710. Language: English. Summary Language: English.

AB We retrospectively examined **HA-1** typing with polymerase chain reaction using sequence-specific primers in 120 samples from 60 HLA-A2-positive Japanese bone marrow transplantation recipients who received short-term methotrexate and cyclosporin A for graft-versus-host disease (GVHD) prophylaxis and their HLA-identical sibling donors. **HA-1**-incompatible pairs were observed in 22% of the samples. The probability of developing acute GVHD (grade II to IV) in **HA-1**-incompatible and -compatible patients was 0% and 19%, respectively (P = .10). In a comparison between **HA-1**-incompatible and -compatible patients with standard-risk leukemia, in whom age, patient/donor sex, and use of a total body irradiation-containing regimen were equivalent, the probability of developing acute GVHD (grade II to IV) was 0% and 10%, respectively (P = .38). No evidence of recurrent leukemia was observed in the **HA-1**-incompatible patients with standard-risk leukemia, compared with 37% in **HA-1**-compatible patients (P =.11). In conclusion, **HA-1** incompatibility may not be a risk factor for grade II to IV acute GVHD in Japanese patients who receive methotrexate and cyclosporin A and undergo bone marrow transplantation from HLA-identical sibling donors.

L7 ANSWER 9 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS

2001:293531 Document No.: PREV200100293531. Effect of disparity in the newly identified **minor histocompatibility antigen** SKH13 on the development of graft-versus-host disease after marrow transplantation from an HLA-identical sibling. Akatsuka, Yoshiki (1); Warren, Edus H.; Brickner, Anthony G.; Lin, Ming-Tseh; Gooly, Ted; Martin, Paul J.; Hansen, John A.; Engelhard, Victor H.; Riddell, Stanley R.. (1) Aichi Cancer Center Research Institute, Nagoya, Aichi Japan. Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 202a. print. Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology. ISSN: 0006-4971. Language: English. Summary Language: English.

AB We have identified a new HLA*0201-restricted **minor histocompatibility antigen** encoded by the KIAA0020 gene and recognized by CD8+ cytotoxic T cells (CTL) derived from a patient with chronic GVHD (Brickner et al, submitted). This antigen, termed HA-8, results from a proline (P) to arginine (R) substitution at position 149 of the KIAA0020 protein (position 1 of the antigenic epitope). Peptides containing both R and P at position 1 bind HLA A201 when pulsed onto cells in vitro but expression of minigene constructs encoding these peptides demonstrated that only the peptide containing R is appropriately processed and transported into the endoplasmic reticulum. KIAA0020 is broadly expressed in tissues with the highest levels in lung and liver. A PCR-RFLP method for genotyping KIAA0020 was developed and a retrospective analysis

donor/recipient pairs previously used for the analysis of **HA-1** disparity (Tseng et al, Blood 94: 2911, 1999) were used for this study. All patients received methotrexate and cyclosporin for GVHD prophylaxis. Of 235 patients, 25 (10.6%) received an HA-8 incompatible transplant and 210 (89.4%) received an HA-8 compatible transplant. Grade II - IV acute GVHD occurred in 12 (48.0%) of the HA-8 incompatible and 45.2 % of the HA-8 compatible recipients (p=.79). Clinical or pathologic chronic GVHD was diagnosed in 18/25 (72%) of incompatible recipients compared with 114/210 (54%) compatible recipients (p=.09). These results suggest a potential association of HA-8 disparity with cGVHD. An HLA A2/HA-8 tetramer has been constructed and is being used prospectively to identify HA-8 specific T cells in blood and tissues after allogeneic BMT.

L7 ANSWER 10 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
2000:168005 Document No.: PREV200000168005. **Minor histocompatibility antigen HA-1** polymorphism in Latin-American caucasoid individuals. Pesoa, S. (1); Borosky, A. (1); Serra, H. (1); Vullo, C. (1). (1) Laboratorio de Inmunogenetica y Diagnostico Molecular, Cordoba Argentina. Human Immunology., (2000) Vol. 61, No. Suppl. 1, pp. S132. Meeting Info.: 14th European Histocompatibility Conference. Montpellier, France April 04-07, 2000 ISSN: 0198-8859. Language: English. Summary Language: English.

L7 ANSWER 11 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
2000:376722 Document No.: PREV200000376722. **Minor histocompatibility antigen HA-1** and the onset of aGVHD in children after unrelated bone marrow transplant. Pizzochero, C. (1); Martinetti, M. (1); Iannone, A. M. (1); Locatelli, F.; Giorgiani, G.; Salvaneschi, L. (1). (1) Serv. Immunohematol. Trasf., IRCCS Policlinico S. Matteo-Pavia, Pavia Italy. Vox Sanguinis, (July, 2000) Vol. 78, No. Suppl. 1, pp. O119. print. Meeting Info.: 26th Congress of the International Society of Blood Transfusion Vienna, Austria July 09-14, 2000 International Society of Blood Transfusion. ISSN: 0042-9007. Language: English. Summary Language: English.

L7 ANSWER 12 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
2000:170423 Document No.: PREV200000170423. Genomic CD31 and **HA-1** polymorphism in HLA matched allogeneic bone marrow graft donor and recipients. Heinemann, F. (1); Ferencik, S. (1); Ottinger, H.; Beelen, D. W.; Schaefer, U. W.; Grosse-Wilde, H. (1). (1) Department of Immunology, University Hospital of Essen, Essen Germany. Human Immunology., (2000) Vol. 61, No. Suppl. 1, pp. S31. Meeting Info.: 14th European Histocompatibility Conference. Montpellier, France April 04-07, 2000 ISSN: 0198-8859. Language: English. Summary Language: English.

L7 ANSWER 13 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
2000:492161 Document No.: PREV200000492282. T cell epitope mapping by **minor histocompatibility antigen** derived peptides and flow cytometry. Eiz-Vesper, B. (1); Blasczyk, R. (1). (1) Department of Transfusion Medicine, Hannover Medical School, Hannover Germany. Human Immunology, (2000) Vol. 61, No. Supplement 2, pp. S1. print. Meeting Info.: 26th Annual Meeting of the American Society for Histocompatibility and Immunogenetics Lake Buena Vista, Florida, USA October 10-14, 2000 American Society for Histocompatibility and Immunogenetics. ISSN: 0198-8859. Language: English. Summary Language: English.

L7 ANSWER 14 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS

HA-1 and the development of acute graft-versus-host disease after allogeneic marrow transplantation. Tseng, Li-Hui; Lin, Ming-Tseh; Hansen, John A.; Gooley, Ted; Pei, Ji; Smith, Anajane G.; Martin, Emily G.; Petersdorf, Effie W.; Martin, Paul J. (1). (1) Fred Hutchinson Cancer Research Center, 1100 Fairview Ave N, D2-100, Seattle, WA, 98109-1024 USA. Blood, (Oct. 15, 1999) Vol. 94, No. 8, pp. 2911-2914. ISSN: 0006-4971. Language: English. Summary Language: English.

AB Results of a previous study suggested that recipient mismatching for the **minor histocompatibility antigen HA-1** is associated with acute graft-versus-host disease (GVHD) after allogeneic marrow transplantation. In that study, most patients received either cyclosporine or methotrexate for GVHD prophylaxis, and a cytotoxic T-cell clone was used to test for **HA-1** disparity. To facilitate large-scale testing, we developed a method that uses genomic DNA to identify **HA-1** alleles. A retrospective study was conducted to correlate **HA-1** disparity and the occurrence of acute GVHD in 237 HLA-A2-positive white patients who had received a marrow or peripheral blood stem cell transplant from an HLA-identical sibling. All patients received both methotrexate and cyclosporine for GVHD prophylaxis. The presence of HLA-A*0201 was confirmed in 34 of the 36 **HA-1** disparate pairs by sequencing the HLA-A locus. Grades II-IV GVHD occurred in 22 (64.7%) of these 34 patients, compared with 86 (42.8%) of the 201patients without **HA-1** disparity (odds ratio, 2.45; 95% confidence interval (CI), 1.15 to 5.23; P = .02). Recipient **HA-1** disparity showed a trend for association with acute GVHD (odds ratio, 2.1; 95% CI, 0.91 to 4.68; P = .08) when a multivariable logistic regression model was used to include additional risk factors. These data are consistent with results of the previous study, suggesting an association between **HA-1** disparity and risk of acute GVHD, but the strength of this association may be lower in patients who received both methotrexate and cyclosporine than in those who received methotrexate or cyclosporine alone.

L7 ANSWER 15 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS

1999:215029 Document No.: PREV199900215029. Feasibility of immunotherapy of relapsed leukemia with ex vivo-generated cytotoxic T lymphocytes specific for hematopoietic system-restricted **minor histocompatibility antigens**. Mutis, Tuna (1); Verdijk, Rob; Schrama, Ellen; Esendam, Bennie; Brand, Anneke; Goulmy, Els. (1) Department of Immunohematology and Blood Bank, Leiden University Medical Center, Bldg 1, E3-Q, 2300 RC, Leiden Netherlands. Blood, (April 1, 1999) Vol. 93, No. 7, pp. 2336-2341. ISSN: 0006-4971. Language: English.

AB Allogeneic bone marrow transplantation (BMT) is a common treatment of hematologic malignancies. Recurrence of the underlying malignancy is a major cause of treatment failure. Donor-derived cytotoxic T lymphocytes (CTLs) specific for patients' **minor histocompatibility antigens** (mHags) play an important role in both graft-versus-host disease (GVHD) and graft-versus-leukemia (GVL) reactivities. mHags **HA-1** and HA-2 induce HLA-A*0201-restricted CTLs in vivo and are exclusively expressed on hematopoietic cells, including leukemic cells and leukemic precursors, but not on fibroblasts, keratinocytes, or liver cells. The chemical nature of the mHags **HA-1** and HA-2 is known. We investigated the feasibility of ex vivo generation of mHag **HA-1**- and HA-2-specific CTLs from unprimed mHag **HA-1**- and/or HA-2-negative healthy blood donors. **HA-1** and HA-2 synthetic peptide-pulsed dendritic cells (DCs) were used as antigen-presenting cells (APC) to stimulate autologous unprimed CD8+ T cells. The ex vivo-generated **HA-1**- and HA-2-specific CTLs efficiently lyse leukemic cells derived from acute myeloid leukemia (AML) and acute lymphoid leukemia (ALL) patients. No

purposes. In conclusion, we present a feasible, novel therapy for the treatment for relapsed leukemia after BMT with a low risk of GVHD.

L7 ANSWER 16 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
2000:167729 Document No.: PREV200000167729. Tetrameric HLA class I-**minor histocompatibility antigen** peptide complexes demonstrate **minor histocompatibility antigen**-specific cytotoxic T lymphocytes in patients with graft-versus-host disease. Mutis, Tuna (1); Gillespie, Geraldine; Schrama, Ellen; Falkenburg, J.H. Frederik; Moss, Paul; Goulmy, Els. (1) The Department of Immunohematology and Blood Bank, Leiden University Medical Center, Albinusdreef 2, 2300 RC, Leiden Netherlands. Nature Medicine., (July, 1999) Vol. 5, No. 7, pp. 839-842. ISSN: 1078-8956. Language: English. Summary Language: English.

AB Graft-versus-host disease (GvHD) is a chief complication of allogeneic bone marrow transplantation. In HLA-identical bone marrow transplantation, GvHD may be induced by disparities in **minor histocompatibility antigens** (mHags) between the donor and the recipient, with the antigen being present in the recipient and not in the donor. Cytotoxic T lymphocytes (CTLs) specific for mHags of the recipients can be isolated from the blood of recipients with severe GvHD (ref. 3). A retrospective study demonstrated an association between mismatch for mHags **HA-1**, -2, -4 and -5 and the occurrence of GvHD in adult recipients of bone marrow from HLA genotypically identical donors. Tetrameric HLA-peptide complexes have been used to visualize and quantitate antigen-specific CTLs in HIV-infected individuals and during Epstein-Barr virus and lymphocytic choriomeningitis virus infections. Here we show the direct ex vivo visualization of mHag-specific CTLs during GvHD using tetrameric HLA-class and I-mHag **HA-1** and HY peptide complexes. In the peripheral blood of 17 **HA-1** or HY mismatched marrow recipients, **HA-1**-and HY-specific CTLs were detected as early as 14 days after bone marrow transplantation. The tetrameric complexes demonstrated a significant increase in **HA-1**- and HY-specific CTLs during acute and chronic GvHD, which decreased after successful GvHD treatment. HLA class I-mHag peptide tetramers may serve as clinical tools for the diagnosis and monitoring of GvHD patients.

L7 ANSWER 17 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
2000:44775 Document No.: PREV200000044775. Effect of disparity for the **minor histocompatibility antigen HA-1** on outcome after marrow transplantation from an HLA-identical sibling. Tseng, L.-H. (1); Hansen, J. A. (1); Lin, M.-T. (1); Gooley, T. (1); Pei, J. (1); Smith, A. G. (1); Goldberg, T. A. (1); Singleton, K. L. (1); Martin, E. G. (1); Petersdorf, E. W. (1); Martin, P. J. (1). (1) Fred Hutchinson Cancer Research Center, Seattle, WA USA. Blood, (Nov. 15, 1999) Vol. 94, No. 10 SUPPL. 1 PART 2, pp. 389b. Meeting Info.: Forty-first Annual Meeting of the American Society of Hematology New Orleans, Louisiana, USA December 3-7, 1999 The American Society of Hematology. ISSN: 0006-4971. Language: English.

L7 ANSWER 18 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
2000:45682 Document No.: PREV200000045682. Genomic typing for the **minor histocompatibility antigen HA-**

Granena,
A.. (1) Alloreactivity Unit, Clinical Hematology Department, Institut Catala d'Oncologia, Barcelona Spain. Blood, (Nov. 15, 1999) Vol. 94, No. 10 SUPPL. 1 PART 2, pp. 365b. Meeting Info.: Forty-first Annual Meeting of
the American Society of Hematology New Orleans, Louisiana, USA December 3-7, 1999 The American Society of Hematology. ISSN: 0006-4971. Language: English.

L7 ANSWER 19 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
2000:43136 Document No.: PREV200000043136. Induction of **HA-1** specific CTL for the treatment of patients after allogenic transplantation. Brossart, P. (1); Spahlinger, B. (1); Grunebach, F. (1); Stuhler, G. (1); Reichardt, V. L. (1); Kanz, L. (1); Brugger, W. (1). (1) Department of Hematology, Oncology and Immunology, University of Tuebingen, Tuebingen Germany. Blood, (Nov. 15, 1999) Vol. 94, No. 10 SUPPL. 1 PART 1, pp. 78a. Meeting Info.: Forty-first Annual Meeting of the
American Society of Hematology New Orleans, Louisiana, USA December 3-7, 1999 The American Society of Hematology. ISSN: 0006-4971. Language: English.

L7 ANSWER 20 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
1999:371048 Document No.: PREV199900371048. Monitoring cytotoxic T lymphocytes specific for **minor histocompatibility antigens** after bone marrow transplantation using tetramers of HLA-class I-mHag peptide complexes. Mutis, Tuna (1); Gillespie, Geraldine; Schrama, Ellen (1); Falkenburg, J. H. Frederik; Moss, Paul; Goulmy, Els (1). (1) Department of Immunohaematology and Blood Bank, University Medical Center,
Leiden Netherlands. British Journal of Haematology, (April, 1999) Vol. 105, No. SUPPL. 1, pp. 32. Meeting Info.: Annual Scientific Meeting of the
British Society for Haematology Brighton, England, UK April 12-15, 1999 British Society for Haematology. ISSN: 0007-1048. Language: English.

L7 ANSWER 21 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
1999:357328 Document No.: PREV199900357328. Genomic identification of the **minor histocompatibility antigen HA-1** locus by allele specific PCR. Wilke, M. (1); Pool, J. (1); den Haan, J. M. M. (1); Goulmy, E. (1). (1) Department of Immunohematology and
Bloodbank, Leiden University Medical Center, Leiden Netherlands. Human Immunology, (1999) Vol. 60, No. SUPPL. 1, pp. S4. Meeting Info.: 13th Conference of the European Federation for Immunogenetics Crete, Greece April 13-17, 1999 European Federation for Immunogenetics. ISSN: 0198-8859.
Language: English.

L7 ANSWER 22 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
1998:135880 Document No.: PREV199800135880. The **minor histocompatibility antigen HA-1**: A diallelic gene with a single amino acid polymorphism. Den Haan, Joke M. M.; Meadows, Leslie M.; Wang, Wei; Pool, Jos; Blokland, Els; Bishop, Tracie L.; Reinhardus, Carla; Shabanowitz, Jeffrey; Offringa, Rienk; Hunt,
Donald F.; Engelhard, Victor H.; Goulmy, Els (1). (1) Dep. Immunohematol. Bloodbank, Leiden Univ. Med. Cent., Albinusdreef 2, 2333 ZA Leiden Netherlands. Science (Washington D C), (Feb. 13, 1998) Vol. 279, No. 5353,
pp. 1054-1057. ISSN: 0036-8075. Language: English.

correlated with the development of severe graft versus host disease (GvHD) after **human** leukocyte antigen-identical bone marrow transplantation. **HA-1** was found to be a nonapeptide derived from an allele of the KIAA0223 gene. The **HA-1**-negative allelic counterpart encoded by KIAA0223 had one amino acid difference from **HA-1**. Family analysis with **HA-1** allele-specific polymerase chain reaction showed an exact correlation between this allelic polymorphism and the **HA-1** phenotype. **HA-1** allele typing of donor and recipient should improve donor selection and allow the determination of bone marrow transplantation recipients with high risk for **HA-1**-induced GvHD development.

L7 ANSWER 23 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS

1998:511549 Document No.: PREV199800511549. **HA-1** and the SMCY-derived peptide FIDSYICQV (H-Y) are immunodominant **minor histocompatibility antigens** after bone marrow transplantation. Rufer, Nathalie; Wolpert, Elisabeth; Helg, Claudine; Tiercy, Jean-Marie; Gratwohl, Alois; Chapuis, Bernard; Jeannet, Michel; Goulmy, Els; Roosnek, Eddy (1). (1) Unite d'Immunol. Transplantation, Hopital Cantonal Univ. Geneve, 24 rue Micheli-du-Crest, CH-1211 Geneve 14 Switzerland. Transplantation (Baltimore), (Oct. 15, 1998) Vol. 66, No. 7, pp. 910-916. ISSN: 0041-1337. Language: English.

AB Background. Allogeneic bone marrow donors can be incompatible at different levels. Even HLA-identical pairs will be still incompatible for numerous **minor histocompatibility antigens** (mHag). Nevertheless, some incompatibilities are found to be associated with an increased risk of graft-versus-host disease (GVHD), which could be related to the way the immune system recognizes these antigens. Methods. We determined the specificity of cytotoxic T-cell clones isolated during acute GVHD or during bone marrow graft rejection in patients (n=14) transplanted with marrow from donors who were histoincompatible for different minor and/or major histocompatibility antigens. Results. We found a clear hierarchy among the different types of histoincompatibilities. In three combinations mismatched for a class I allele, all 27 clones isolated during GVHD were specific for the incompatible HIA molecule. In the 11 class I-identical combinations, 14 different mHags were recognized. The mHag **HA-1**, known to have a significant impact on the development of GVHD, was recognized in the two HA-1incompatible combinations. In one of these combinations, which was sex mismatched, all 56 clones analyzed were directed against **HA-1**, demonstrating the dominance of this mHag. In the four **HA-1**-compatible, sex-mismatched combinations, the anti-H-Y response was directed against one immunodominant epitope rather than against multiple Y-chromosome encoded epitopes. All male specific cytotoxic T lymphocytes (n=15) recognized the same high-performance liquid chromatography-purified peptide fraction presented by T2 cells. Moreover, all cytotoxic T lymphocytes tested (n = 6) were specific for the SMCY-derived peptide FIDSYICQV, originally described as being the H-Y epitope recognized in the context of HLA-A*0201. Conclusions. Some histocompatibility antigens are recognized in an immunodominant fashion and will therefore be recognized in the majority of mismatched combinations. Only for such antigens, correlations between mismatches and the occurrence of GVHD or graft rejections will be found.

L7 ANSWER 24 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS

antigens before allogeneic bone marrow transplantation. Rufer, N.; Starobinski, M.; Chapuis, B.; Gratwohl, A.; Jeannet, M.; Helg, C.; Roosnek, E. (1). (1) Unite Immunol. Transplantation, Hop. Cantonal Univ. Geneve, 24 rue Micheli-du-Crest, CH-1211 Geneve 4 Switzerland. Bone Marrow Transplantation, (Nov. 1, 1998) Vol. 22, No. 9, pp. 895-898. ISSN: 0268-3369. Language: English.

AB To study sensitisation to **minor histocompatibility antigens** (mHag) before and after BMT, we measured antidonor CTL activity in five patients who had rejected their graft, and in a control group of 10 leukemic patients who engrafted without complications. All patients were transplanted with marrow from an HLA-identical sibling. Fourteen patients were conditioned with cyclophosphamide (120 mg/kg) and TBI (1350 cGy) and received a T cell-depleted graft, while one patient with aplastic anaemia received cyclophosphamide alone and unmanipulated marrow. Before transplantation, anti-donor CTL activity was detected in two of the 15 patients. These patients rejected their grafts at days 21 and 58, respectively. In the other three patients who rejected their grafts at days 41, 60 and 250, CTL activity was found only after transplantation. In contrast, no anti-donor CTLs could be detected at any time in the 10 patients who engrafted permanently. We have identified some of the mHags recognised during graft rejection by cloning and subsequent specificity analysis of the recipient CTLs. In the patient who rejected at day 41 without detectable immunization before BMT, the response was directed against **HA-1**, a minor antigen known to play a role in GVHD. In the other combinations, a significant part of the CTL activity was directed against the male antigen H-Y. In the patient who rejected the marrow of her HLA-identical brother at day 250, two clones recognised H-Y, while five others recognised at least three distinct autosomal mHags. This patient had an HLA-identical sister who expressed only one autosomal mHag that had been recognised by one single T cell clone. After re-transplantation with the marrow of this second donor, the CTL activity could no longer be detected and the patient engrafted without further complications.

L7 ANSWER 25 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS

1999:101514 Document No.: PREV199900101514. Correlation between disparity for the **minor histocompatibility antigen HA-1** and the development of graft-versus-host disease following allogeneic marrow transplantation. Tseng, L.-H.; Martin, P. J.; Lin, M.-T.; Gooley, T.; Pei, J.; Smith, A. G.; Petersdorf, E.; Hansen, J. A.. Fred Hutchinson Cancer Res. Cent., Seattle, WA USA. Blood, (Nov. 15, 1998) Vol. 92, No. 10 SUPPL. 1 PART 1-2, pp. 448A. Meeting Info.: 40th Annual Meeting of the American Society of Hematology Miami Beach, Florida, USA December 4-8, 1998 The American Society of Heamatology. ISSN: 0006-4971. Language: English.

L7 ANSWER 26 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS

1998:510825 Document No.: PREV199800510825. Genomic identification of the **minor histocompatibility antigen HA-1** locus by allele-specific PCR. Wilke, M. (1); Pool, J.; Den Haan, J. M. M.; Goulmy, E.. (1) Dep. Immunohematol. Bloodbank, Leiden Univ. Med. Cent., Albinusdreef 2, 2333 ZA Leiden Netherlands. Tissue Antigens, (Oct., 1998) Vol. 52, No. 4, pp. 312-317. ISSN: 0001-2815. Language: English.

AB Graft-versus-host disease (GvHD) can be a major complication of allogeneic

between donor and recipient are a potential risk for the development of GvHD, A mismatch for the mHag **HA-1** can cause GvHD in adult recipients of allogeneic bone marrow from HLA-identical donors. The mHag HA1, first identified by HLA-A*0201-restricted cytotoxic T cells (CTLs), was recently chemically characterized as a nonapeptide. On the cDNA level, the **HA-1** locus has two alleles, HA-1H and HA-1R, which differ in two nucleotides, resulting in a single amino acid substitution. Here we report on the genomic structure of the **HA-1** locus. Isolation and sequencing of cosmid DNA encoding the **HA-1** peptide sequence revealed that the **HA-1** alleles are encoded by two exons. Two different primer sets were designed, each consisting of allele-specific primers and a common primer, and both sets containing intronic sequences We performed genomic DNA typing of three families consisting of 24 HLA-A*0201-positive individuals.

The predicted allele-specific products correlated in all cases with the mHag classification by CTLs and by RT-PCR. We demonstrate for the first time the genomic identification of the mHag **HA-1** locus. Prospective genomic typing for the **HA-1** alleles will improve donor selection and identify HLA-A*0201-positive recipients with a high risk for **HA-1**-induced GvHD.

L7 ANSWER 27 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS

1998:510824 Document No.: PREV199800510824. Definition of the gene encoding the **minor histocompatibility antigen** **HA-1** and typing for **HA-1** from genomic DNA. Tseng, L.-H.; Lin, M.-T.; Martin, P. J.; Pei, J.; Smith, A. G.; Hansen, J. A. (1). (1) Fred Hutchinson Cancer Res. Cent., 1100 Fairview Ave. N. D2-100, P.O. Box 19024, Seattle, WA 98109-1024 USA. Tissue Antigens, (Oct., 1998) Vol. 52, No. 4, pp. 305-311. ISSN: 0001-2815. Language: English.

AB Recipient mismatching for the **minor histocompatibility antigen** **HA-1** has been associated with acute graft-versus-host disease after allogeneic marrow transplantation. Two polymorphic nucleotides near an exon-intron junction of the gene encoding this **minor histocompatibility antigen** have been identified. In this study, we determined the genomic DNA sequence of the intron downstream from this polymorphic exon. Based on this sequence, primers were designed to amplify the genomic **HA-1** gene sequence, and analysis of restriction fragment length polymorphisms was used to assign the **HA-1** genotypes of 160 unrelated probands and a paired sibling for each proband. Among probands, the HA-1H allele frequency was 0.441, and the HA-1R allele frequency was 0.559. The distribution of **HA-1** genotypes showed close fit with Hardy-Weinberg equilibrium. Likewise, the number of sibling pairs with disparity for **HA-1** alleles showed close fit with predictions based on Hardy-Weinberg equilibrium. These results provide a simple and well validated method for future studies correlating **HA-1** disparity with clinical outcome after allogeneic marrow transplantation.

L7 ANSWER 28 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS

1998:471164 Document No.: PREV199800471164. Higher risk of immunodominant incompatibility for **HA-1, minor histocompatibility antigen**. Maruya, E. (1); Saji, H. (1); Yokoyama, S. (1); Ito, K.; Goulmy, E.; Juji, T.. (1) Dep. Res., Kyoto Red Cross Blood Cent., Kyoto Japan. Human Immunology, (1998) Vol. 59, No. SUPPL. 1, pp. 95. Meeting Info.: 24th Annual Meeting of the American Society for Histocompatibility and Immunogenetics Vancouver, British Columbia, Canada October 10-15, 1998 American Society for Histocompatibility and Immunogenetics. ISSN: 0198-8859. Language: English.

1997:392547 Document No.: PREV199799691750. How much benefit can be expected from matching for minor antigens in allogeneic marrow transplantation. Martin, P. J.. Fred Hutchinson Cancer Res. Cent., 1124 Columbia St., Seattle, WA 98104 USA. Bone Marrow Transplantation, (1997) Vol. 20, No. 2, pp. 97-100. ISSN: 0268-3369. Language: English.

AB The presence of recipient disparity for a **minor histocompatibility antigen** termed **HA-1** is associated with an increased risk of grades II-IV GVHD after marrow transplantation from an HLA-identical sibling. These data offer an opportunity to test the validity of theoretical models suggesting that the minor antigens capable of eliciting GVHD in any given individual are encoded by approximately seven genetic loci. Published data and theoretical models agree that there is little benefit to be gained by typing and matching at a single locus. The models predict, however, that substantial benefit would be possible if multiple loci could be typed. The success of matching would be enhanced by the availability of assays that would allow typing for at least four of the loci encoding antigens that could cause GVHD in any given individual.

L7 ANSWER 30 OF 38 MEDLINE DUPLICATE 1

97080610 Document Number: 97080610. PubMed ID: 8921955. Conservation of **minor histocompatibility antigens** between **human** and non-**human primates**. den Haan J M; Bontrop R E; Pool J; Sherman N; Blokland E; Engelhard V H; Hunt D F; Goulmy E. (Department of Immunohaematology and Bloodbank, Leiden University Hospital, The Netherlands.. haan.j@rulgca.leidenuniv.nl) . EUROPEAN JOURNAL OF IMMUNOLOGY, (1996 Nov) 26 (11) 2680-5. Journal code: EN5; 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB It is well accepted that **minor histocompatibility antigens** (mHag) can function as transplantation barriers between HLA-matched individuals. Little is known about the molecular nature and evolutionary conservation of mHag. It is only very recently that the first **human** mHag were identified. The HLA-A2.1-restricted mHag HA-2 and the HLA-B7-restricted mHag H-Y appeared to be peptides derived from polymorphic self proteins. Here we show that the HLA-A2.1-restricted mHag **HA-1**, HA-2, and the H-Y peptides are conserved between man, chimpanzees and rhesus macaques. **Human** cytotoxic T cell clones specific for the HLA-A2.1-restricted mHag **HA-1**, HA-2, and H-Y recognized HLA-A2.1 gene-transfected chimpanzee and rhesus macaque cells. High-pressure liquid chromatography fractionation of HLA-A2.1-bound peptides isolated from the HLA-A2.1-transfected chimpanzee cells revealed that the chimpanzee **HA-1** and HA-2 co-eluted with the **human HA-1** and HA-2. Subsequent amino acid sequencing showed that the chimpanzee HA-2 peptide is identical to the **human** HA-2 peptide. Our functional and biochemical results demonstrate that mHag peptides are conserved for over 35 million years.

L7 ANSWER 31 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS

1996:111037 Document No.: PREV199698683172. Mismatches of **minor histocompatibility antigens** between HLA-identical donors and recipients and the development of graft-versus-host disease after bone marrow transplantation. Goulmy, Els (1); Schipper, Ronald; Pool, Jos; Blokland, Els; Falkenburg, J. H. Frederick; Vossen, Jaak; Gratwohl, Alois; Vogelsang, Georgia B.; Van Houwelingen, Hans C.; Van Rood, Jon J.. (1)

No. 5, pp. 281-285. ISSN: 0028-4793. Language: English.
AB Background. Graft-versus-host disease (GVHD) can be a major complication of allogeneic bone marrow transplantation even when the donor and recipient are siblings and share identical major histocompatibility antigens. The explanation may be a mismatch of **minor histocompatibility antigens**. We previously characterized five **minor histocompatibility antigens, HA-1**, 2, 3, 4, and 5, that are recognized by T cells in association with the major histocompatibility antigens HLA-A1 and A2. Methods. We collected peripheral-blood leukocytes from 148 bone marrow recipients and their sibling donors, who were genotypically HLA identical. Fifty pairs were positive for HLA-A1, 117 were positive for HLA-A2, and 19 were positive for both. The pairs were typed with cytotoxic-T-cell clones specific for **minor histocompatibility antigens HA-1**, 2, 3, 4, and 5. Results. Mismatches of HA-3 were equally distributed among recipients in whom GVHD developed and those in whom it did not. By contrast, a mismatch of only **HA-1** was significantly correlated with GVHD of grade II or higher (odds ratio, infin ; P=0.02) in adults. One or more mismatches of **HA-1**, 2, 4, and 5 were also significantly associated with GVHD (odds ratio, infin ; P=0.006) in adults. These associations were not observed in children. Conclusions. A mismatch of **minor histocompatibility antigen HA-1** can cause GVHD in adult recipients of allogeneic bone marrow from HLA-identical donors. Prospective **HA-1** typing may improve donor selection and identify recipients who are at high risk for GVHD.

L7 ANSWER 32 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
1995:294021 Document No.: PREV199598308321. Interindividual Conservation of T-Cell Receptor beta Chain Variable Regions by **Minor Histocompatibility Antigen**-Specific HLA-A*0201-Restricted Cytotoxic T-Cell Clones. Goulmy, Els (1); Pool, Jos; Van Den Elsen, Peter J.. (1) Dep. Immunohaematol., Univ. Hosp. Leiden, Bldg. 1-3Q, PO Box 9600, 2300 RC Leiden Netherlands. Blood, (1995) Vol. 85, No. 9, pp. 2478-2481. ISSN: 0006-4971. Language: English.
AB **Minor histocompatibility antigens** (mHags) are involved in the induction of graft-versus-host disease (GVHD) after HLA-identical bone marrow transplantation. Previously, we isolated a series of HLA-A*0201-restricted cytotoxic T-cell (CTL) clones specific for the same mHag **HA-1** from peripheral blood of three unrelated patients who were suffering from GVHD. We have now analyzed the composition of the T-cell receptor (TCR) V regions of 12 of these mHag **HA-1**-specific HLA-A*0201-restricted CTL clones by DNA sequencing of the alpha and beta chains. Of these 12 clones, derived from three unrelated individuals, five independent TCR-alpha-V- and beta-V-region sequences were established. The TCR-alpha chains were composed of varying TCR-alpha-V and TCR-alpha-J genes with no obvious similarities in structure in the N regions. However, the TCR-beta chains all used the TCR-beta-V6S9 gene segment, and showed remarkable similarities within the N-D-N regions; ie, three independent beta-chain sequences (originating from donors Ha and Gy) shared a leucine/valine amino acid pair, whereas the other two (originating from donors Ha and Wi) shared a serine/threonine pair, all at positions 99 and 100 of the TCR-beta-V region. In conclusion, the TCR analysis of HA1 mHag-specific

L7 ANSWER 33 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
1995:441494 Document No.: PREV199598455794. Recognition of clonogenic leukemic
cells, remission bone marrow and HLA-identical donor bone marrow by CD8+ or CD4+ **minor histocompatibility antigen**
-specific cytotoxic T lymphocytes. Faber, Laura M. (1); Van Der Hoeven, John; Goulmy, Els; Hooftman-Den Otter, Annelies L.; Van Luxemburg-Heijs, Simone A. P.; Willemze, Roel; Falkenburg, J. H. Frederik. (1) Dep. Hematol., Build. 1, C2-R, Univ. Med. Cent., P.O. 9600, 2300 RC Leiden Netherlands. Journal of Clinical Investigation, (1995) Vol. 96, No. 2, pp.
877-883. ISSN: 0021-9738. Language: English.

AB We investigated whether minor histocompatibility (mH) antigen-specific cytotoxic T lymphocytes (CTL) can discriminate between leukemic hematopoietic progenitor cells (leukemic-HPC) from AML or CML patients, the HPC from their remission bone marrow (remission-HPC), and normal HPC from their HLA-identical sibling bone marrow donor (donor-HPC). Specific lysis by CD8+ CTL clones was observed not only of the leukemic-HPC but also of the donor-HPC in 3/4 patient/donor combinations expressing mH antigen **HA-1**, 3/5 combinations expressing mH antigen HA2, 2/3 combinations expressing mH antigen HA-3, and 2/2 combinations expressing mH antigen HY-A1. In four patient/donor combinations the recognition of the donor-HPC was clearly less than of the leukemic-HPC, indicating differential susceptibility to lysis by these mH CTL clones. In
addition, differential recognition of leukemic-HPC and remission-HPC within seven patients was analyzed. In one patient expressing the HA-2 antigen on the leukemic cells the recognition of the remission-HPC was clearly less than of the leukemic-HPC. One CD4+ CTL clone showed specific lysis of the leukemic-HPC from an AML patient and a CML patient as well as
of normal remission-HPC and donor-HPC. These results illustrate that in general CD8+ and CD4+ mH antigen specific CTL clones do not differentially
recognize leukemic-HPC and normal-HPC. However, differences in susceptibility to lysis of malignant versus normal cells may contribute to
a differential GVL effect.

L7 ANSWER 34 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
1994:163243 Document No.: PREV199497176243. Recognition of **minor histocompatibility antigens** on lymphocytic an myeloid
leukemic cells by cytotoxic T-cell clones. Van Der Harst, Dick; Goulmy, Els; Falkenburg, J. H. Frederik; Kooij-Winkelaar, Yvonne M. C.; Van Luxemburg-Heijs, Simone A. P.; Goselink, Henriette M. (1); Brand, Anneke. (1) Dep. Immunohematol. Bloodbank, Univ. Med. Cent. Leiden, Build. 1, E3-Q, PO Box 9600, 2300 RC Leiden Netherlands. Blood, (1994) Vol. 83, No. 4, pp. 1060-1066. ISSN: 0006-4971. Language: English.

AB Clinical studies indicated an enhanced antileukemic effect of allogeneic bone marrow transplantation (BMT), as compared with autologous BMT. After allogeneic HLA-identical BMT, donor-derived cytotoxic T lymphocytes (CTLs)
directed at minor histocompatibility (mH) antigens on the recipients, tissues can be shown. To evaluate the antileukemic reactivity of mH antigen-specific CTLs, we analyzed the expression of mH antigens on circulating lymphocytic and myeloid leukemic cells. We show that the defined mH specificities **HA-1** through HA-5 and H-Y are
present on leukemic cells, indicating that mH antigen-specific CTLs are capable of HLA class I-restricted antigen-specific lysis of leukemic cells. Compared with interleukin-2-stimulated normal lymphocytes, leukemic

clone. A possible explanation for this phenomenon is impaired expression of the LFA-1 adhesion molecule. Our study suggests that mH antigen-specific HLA class I-restricted CD8+ CTLs may be involved in the graft-versus-leukemia reactivity after allogeneic BMT.

L7 ANSWER 35 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
1994:76924 Document No.: PREV199497089924. **Minor histocompatibility antigens HA-1-**, -2-, and -4-, and HY-specific cytotoxic T-cell clones inhibit **human** hematopoietic progenitor cell growth by a mechanism that is dependent on direct cell-cell contact. Marijt, W. A. F. (1); Veenhof, W. F. J.; Goulmy, E.; Willemze, R.; Van Rood, J. J.; Falkenburg, J. H. F.. (1) Dep. Hematology, Build. 1, C2-R, Univ. Med. Center, Rijnsburgerweg 10, 2333 AA Leiden Netherlands. Blood, (1993) Vol. 82, No. 12, pp. 3778-3785. ISSN: 0006-4971. Language: English.

AB HLA-identical bone marrow transplantation (BMT) may be complicated by graft-versus-host disease or graft rejection. Both complications are thought to be initiated by recognition of minor histocompatibility (mH) antigens by HLA-restricted mH-antigen-specific T lymphocytes. Using HLA-A2-restricted mH antigens **HA-1**-, -2-, and -4-, and HY-specific cytotoxic T lymphocyte (CTL) clones, we studied the recognition by these CTL clones of interleukin-2 (IL-2)-stimulated T cells (IL-2 blasts), BM mononuclear cells (BMMNCs), and hematopoietic progenitor cells (HPCs). We showed that, when IL-2 blasts from the BM donors who were investigated were recognized by the HA1-, -2-, and -4-, and HY-specific CTL clones, their BMMNCs and HPCs were recognized as well by these CTL clones, resulting in antigen-specific growth inhibition of erythrocyte burst-forming units (BFU-E), colony-forming units-granulocyte (CFU-G), and CFU-macrophage (CFUM). The HA-2-specific CTL clone, however, inhibited BFUE and CFU-G growth from four donors to a lesser extent than from two other donors. We further investigated whether inhibitory cytokines released into the culture medium by the antigen-specific stimulated CTLs or by stimulated BMMNCs were responsible for suppression of HPC growth or whether this effect was caused by direct cell-cell contact between CTLs and HPCs. HPC growth inhibition was only observed after preincubation of BMMNCs and CTLs together for 4 hours before plating the calls in semisolid HPC culture medium. When no cell-cell contact was permitted before plating, neither antigen-stimulated CTL nor antigen-nonstimulated CTLs provoked HPC growth inhibition. Culturing BMMNCs in the presence of supernatants harvested after incubation of BMMNCs and CTL clones together for 4 or 72 hours did also not result in HPC growth inhibition. Both suppression of HPC growth and lysis of IL-2 blasts and BMMNCs in the 51Cr-release assay appeared to be dependent on direct cell-cell contact between target cells and CTLs and were not caused by the release of inhibitory cytokines into the culture medium by antigen-specific stimulated CTLs or by stimulated BMMNCs. Our results show that mH-antigen-specific CTLs can inhibit HPC growth by a direct cytolytic effect and may therefore be responsible for BM graft rejection after HLA-identical BMT.

L7 ANSWER 36 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
1994:62114 Document No.: PREV199497075114. Multiple **minor histocompatibility antigen** disparities between a recipient and four HLA-identical potential sibling donors for bone marrow transplantation. Marijt, Erik A. F. (1); Veenhof, Willy F. J.; Goulmy, Els; Kluck, Petra M. C.; Brand, Anneke; Willemze, Roel; Van Rood, John J.;

(1993) Vol. 37, No. 4, pp. 221-228. ISSN: 0198-8859. Language: English.
AB A patient with acute leukemia and her family including four HLA-identical siblings were analyzed to select a donor who was not only HLA- but also minor histocompatibility (mH) antigen compatible for allogeneic bone marrow transplantation (BMT). The HLAA2 restricted mH antigen-specific **HA-1**, -2, -4, and -5 cytotoxic T-lymphocyte (CTL) clones were used to type the family members for expression of these mH antigens. The patient and one HLA-identical sibling were compatible for these mH antigens. This sibling was selected as the bone marrow donor. The patient engrafted promptly but developed acute and chronic graft-versus-host disease. To study the presence of other mH antigen disparities between recipient and donor, host-versus-graft CTL lines and clones were generated by stimulation of recipient peripheral blood lymphocytes (PBLs) with donor bone marrow cells, and graft-versus-host CTL lines were generated after BMT by stimulation of PBLs of donor origin with recipient bone marrow cells. These CTL lines were cytotoxic to cells from the bone marrow donor and from the recipient, respectively, and to cells from several other family members. T-cell lines, generated from the patient after BMT by stimulation of recipient-derived PBLs with donor bone marrow cells, exhibited no specific cytotoxicity to donor or recipient cells. Chimerism studies after BMT revealed that the PBLs and T-cell lines generated after BMT were of donor origin. CTL lines that were generated from PBLs from the three other HLA-identical siblings in this family by stimulation with HLA-identical donor bone marrow cells also exhibited cytotoxicity to cells from several family members. Our results show that in addition to compatibility for **HA-1**, -2, -4, and -5 between the recipient and the donor, other mH antigen disparities existed between all HLA-identical siblings, illustrating the high degree of polymorphism of mH antigens and therefore the difficulty of finding mH antigen-compatible donor-recipient pairs even when more than one HLA-identical sibling is present within a family.

L7 ANSWER 37 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
1993:388097 Document No.: PREV199396063397. A genetic analysis of **human minor histocompatibility antigens** demonstrates mendelian segregation independent of HLA.
Schreuder, Geziena M. T.; Pool, Jos; Blokland, Els; Van Els, Cecile; Bakker, Astrid; Van Rood, Jon J.; Goulmy, Els (1). (1) Dep. Immunohaematol. Blood Bank, Univ. Hosp. Leiden, P.O. Box 9600, 23000 RC Leiden Netherlands. Immunogenetics, (1993) Vol. 38, No. 2, pp. 98-105. ISSN: 0093-7711. Language: English.
AB An analysis of the genetic traits of **human** minor histocompatibility (mH) antigens is, unlike with inbred mice, rather complicated. Moreover, the fact that mH antigens are recognized in the context of MHC molecules creates an additional complication for reliable segregation analysis. To gain insight into the mode of inheritance of the mH antigens, we relied upon a series of HLA-A2-restricted cytotoxic T-cell (CTL) clones specific for four mH antigens. To perform segregation analysis independent of HLA-A2, we transfected HLA-A2-negative cells with the HLA-A2 gene: this results in the cell surface expression of the HLA-A2 gene product and, if present, mH antigen recognition. The mode of inheritance of the HLA-A2-restricted mH antigens **HA-1**, -2, -4, and -5 was analyzed in 25 families whose members either naturally expressed HLA-A2 or were experimentally rendered HLA-A2-positive. Analysis

demonstrated that the four mH antigens behaved as Mendelian traits, whereby each can be considered a product of a gene with two alleles, one expressing and one not expressing the detected specificity. We also showed that the loci encoding the **HA-1** and HA-2 antigens are not closely linked to HLA (lod scores Z (0-0.05) lt -4.0). Some indication was obtained that the HA-4- and HA-5-encoding loci may be losely linked to HLA. While we are aware of the limited results of this nonetheless comprehensive study, we feel the similarity in immunogenetic traits between **human** and mouse mH antigens is at least striking.

L7 ANSWER 38 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
1993:51796 Document No.: PREV199395028098. Tissue distribution of **human minor histocompatibility antigens**: Ubiquitous versus restricted tissue distribution indicates heterogeneity among **human** cytotoxic T lymphocyte-defined non-MHC antigens. De Bueger, Marleen (1); Bakker, Astrid; Van Rood, Jon J.; Van Der Woude, Fokko; Goulmy, Els. (1) Dep. Immunohaematol. Bloodbank, Room L3-37, University Hospital Leiden, Rijsburgerweg 10, 2333 AA Leiden Netherlands. Journal of Immunology, (1992) Vol. 149, No. 5, pp. 1788-1794. ISSN: 0022-1767. Language: English.
AB We determined the tissue distribution of 7 **human** minor histocompatibility (H) Ag. Each of these Ag is defined by one or more MHC class I-restricted CTL clones, previously generated from PBL primed against minor H Ag by HLA-identical bone marrow transplantation (BMT). CTL-mediated lysis of tissue-derived cells and cultured cell lines was used as an in vitro assay for minor H Ag expression of several **human** tissues. The Ag HA-3 (HLA-A1-restricted), HA-4 (HLA-A2 restricted), HA-6 and HA-7 (HLA-B7 restricted), and the male-specific Ag H-Y (HLA-A2 and B7 restricted) were found to be expressed on cells of all tissues tested. In contrast, the HLA-A2-restricted Ag **HA-1** and HA-2 were demonstrated on PHA-blasts, EBV-BLCL, purified T cells, B cells, monocytes, and immature thymocytes, but could not be demonstrated on skin-derived cultured fibroblasts, keratinocytes, melanocytes, cultured epithelial cells of kidney proximal tubili, and umbilical cord vein-derived endothelial cells. Incubation of the latter cell lines with rIFN-gamma, rTNF-alpha, and/or rIL-1-alpha, in concentrations shown to maximally increase their susceptibility to lysis by allo-MHC class I CTL, did not induce recognition by **HA-1**- and HA-2-specific CTL in vitro. These results indicate an ubiquitous tissue expression of the minor H Ag HA-3, -4, -6, -7 and H-Y in contrast to the hemopoietic cell lineage-restricted expression for **HA-1** and HA-2. The heterogeneity in tissue expression of T cell defined, class I-restricted non-MHC Ag implies that they might be derived from intracellular proteins with either an ubiquitous or a more specialized cell type-specific function.

=> s "VLHDDLLEA" or "VLRDDLLEA"

L10 8 "VLHDDLLEA" OR "VLRDDLLEA"

=> dup remove l10

PROCESSING COMPLETED FOR L10
L11 2 DUP REMOVE L10 (6 DUPLICATES REMOVED)

=> d l11 1-2 cbib abs

L11 ANSWER 1 OF 2 MEDLINE DUPLICATE 1
2000166344 Document Number: 20166344. PubMed ID: 10703604. Molecular modeling of the minor histocompatibility antigen HA-1 peptides binding to HLA-A alleles. Ren E C; Kangueane P; Kolatkar P; Lin M T; Tseng L H; Hansen J A. (Department of Microbiology, WHO Collaborating Center for Immunology, National University of Singapore, Singapore.. micrenec@nus.edu.sg) . TISSUE ANTIGENS, (2000 Jan) 55 (1) 24-30. Journal code: VSV; 0331072. ISSN: 0001-2815. Pub. country: Denmark. Language: English.

AB Mismatch of the minor histocompatibility antigen HA-1 has been shown to correlate with graft-versus-host disease in HLA-matched sibling marrow transplants. The HA-1H peptide (**VLHDDLLEA**) that generates this response is known to be presented by HLA-A*0201. In order to understand the interaction of HA-1 peptides with other HLA-A alleles, we have used the LOOK interface to construct molecular models of both HA-1H peptide (**VLHDDLLEA**) and HA-1R peptide (**VLRDDLLEA**) binding with 103 HLA-A alleles. The results show that in addition to A*0201, 21/103 other HLA-A alleles should be able to bind HA-1H peptide but not HA-1R peptide. Based on the modeled predictions, HLA alleles can be categorised into 4 groups with respect to their interaction with HA-1 peptides: Group 1 - bind HA-1H peptide but not HA-1R peptide; Group 2 - bind HA-1R peptide but not HA-1H peptide; Group 3 - bind both HA-1H and HA-1R peptides; Group 4 - bind neither peptide. These predicted binding patterns of HA-1 peptides will be useful as an aid for defining a wider pool of HLA-A alleles in which HA-1 disparities among donor-recipient pairs can be investigated.

L11 ANSWER 2 OF 2 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 2
1999342032 EMBASE Clinical potential of the HA-1 peptide, a minor histocompatibility antigen. Expert Opinion on Therapeutic Patents 9/10 (1437-1441) 1999.
Refs: 25.
ISSN: 1354-3776. CODEN: EOTPEG. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Minor histocompatibility (H) antigens are the targets of host versus graft (HVG), graft versus host (GVH) and graft versus leukaemia (GVL) immune responses following transplantation of organs or tissues between donor/recipient pairs matched for transplantation antigens encoded by the major histocompatibility complex (MHC: HLA in humans). There is a particular clinical problem in predicting and treating GVH disease, which occurs in a significant proportion of bone marrow transplant (BMT) patients, even those with HLA-identical sibling donors. However, many of these recipients receive BMT as part of the treatment for leukaemia and there is a correlation in them between harmful GVH and potentially therapeutic GVL, implying the same target antigens. The molecular identity of minor H antigens is therefore a key issue. This patent describes the recent identification of one of the human minor H antigen (HA-1) and proposes methods for using the nonameric peptide identified, **VLHDDLLEA**, or analogues of it, to modulate HVG and GVH responses, to promote GVL and, with knowledge of the polymorphism of the encoding gene, to type BMT recipients and their potential donors for presence of the antigen.

=> s (goulmy e?/au or hunt d?/au or engelhard v?/au)

L12 6050 (GOULMY E?/AU OR HUNT D?/AU OR ENGELHARD V?/AU)

MISSING OPERATOR L12 MINOR
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l12 and minor histocompatibility antigen

3 FILES SEARCHED...
L13 274 L12 AND MINOR HISTOCOMPATIBILITY ANTIGEN

=> dup remove l13

PROCESSING COMPLETED FOR L13
L14 121 DUP REMOVE L13 (153 DUPLICATES REMOVED)

=> s l14 and HA-1

L15 36 L14 AND HA-1

=> dup remove l15

PROCESSING COMPLETED FOR L15
L16 36 DUP REMOVE L15 (0 DUPLICATES REMOVED)

=> d l16 cbib abs

L16 ANSWER 1 OF 36 SCISEARCH COPYRIGHT 2001 ISI (R)
2001:401714 The Genuine Article (R) Number: 421ZZ. Interindividual conservation of T-cell receptor beta-chain variable region (tcrbv) repertoire by in vitro generated **minor histocompatibility antigen ha-1** -specific Cytotoxic T-cells (CTL's). Verdijk R M (Reprint); Mutis T; Kamp J; Schrama E; Brand A; Wilke M; **Goulmy E.** BONE MARROW TRANSPLANTATION (MAR 2001) Vol. 27, Supp. [1], pp. S111-S111. Publisher: NATURE PUBLISHING GROUP. HOUNDMILLS, BASINGSTOKE RG21 6XS, HAMPSHIRE, ENGLAND. ISSN: 0268-3369. Language: English.

=> d l16 1-36 cbib abs

L16 ANSWER 1 OF 36 SCISEARCH COPYRIGHT 2001 ISI (R)
2001:401714 The Genuine Article (R) Number: 421ZZ. Interindividual conservation of T-cell receptor beta-chain variable region (tcrbv) repertoire by in vitro generated **minor histocompatibility antigen ha-1** -specific Cytotoxic T-cells (CTL's). Verdijk R M (Reprint); Mutis T; Kamp J; Schrama E; Brand A; Wilke M; **Goulmy E.** BONE MARROW TRANSPLANTATION (MAR 2001) Vol. 27, Supp. [1], pp. S111-S111. Publisher: NATURE PUBLISHING GROUP. HOUNDMILLS, BASINGSTOKE RG21 6XS, HAMPSHIRE, ENGLAND. ISSN: 0268-3369. Language: English.

L16 ANSWER 2 OF 36 SCISEARCH COPYRIGHT 2001 ISI (R)
2001:401709 The Genuine Article (R) Number: 421ZZ. Efficient in vitro induction of **minor histocompatibility antigen HA-1** specific cytotoxic T-cells using dendritic cells retrovirally transduced with **HA-1** coding cDNA. Mutis T (Reprint); Ghoreschi K; Schrama E; Kamp J; Heemskerk M; Falkenburg J H F; **Goulmy E.** BONE MARROW TRANSPLANTATION (MAR 2001) Vol. 27, Supp. [1], pp. S110-S110. Publisher: NATURE PUBLISHING GROUP. HOUNDMILLS,

L16 ANSWER 3 OF 36 SCISEARCH COPYRIGHT 2001 ISI (R)
2001:401523 The Genuine Article (R) Number: 421ZZ. Induction of hematopoiesis-specific **minor histocompatibility antigen** (mHag) **HA-1** and HA-2 specific CD8+T-cells after Donor Lymphocyte Infusion (DLI) for relapsed CML associated with complete molecular remission. Marijt W A F (Reprint); Kester M G D M; **Goulmy E**; Mutis T; Drijfhout J W; Willemze R; Falkenburg J H F. BONE MARROW TRANSPLANTATION (MAR 2001) Vol. 27, Supp. [1], pp. S23-S24. Publisher: NATURE PUBLISHING GROUP. HOUNDMILLS, BASINGSTOKE RG21 6XS, HAMPSHIRE, ENGLAND. ISSN: 0268-3369. Language: English.

L16 ANSWER 4 OF 36 SCISEARCH COPYRIGHT 2001 ISI (R)
2001:401521 The Genuine Article (R) Number: 421ZZ. RNA expression of the **minor histocompatibility antigen HA-1** is restricted to hematopoietic cells; relevance for immunotherapy of hematological malignancies. Wilke M (Reprint); Dolstra H; Maas F; Pool J; Brouwer R; Falkenburg J H F; Rebello A; Lamers F; Schuuring E; Kluin P; Brasseur F; **Goulmy E**. BONE MARROW TRANSPLANTATION (MAR 2001) Vol. 27, Supp. [1], pp. S23-S23. Publisher: NATURE PUBLISHING GROUP. HOUNDMILLS, BASINGSTOKE RG21 6XS, HAMPSHIRE, ENGLAND. ISSN: 0268-3369. Language: English.

L16 ANSWER 5 OF 36 SCISEARCH COPYRIGHT 2001 ISI (R)
2001:401479 The Genuine Article (R) Number: 421ZZ. Generation of allo-HLA restricted **minor histocompatibility antigen HA-1** specific cytotoxic T-cells (CTLs) as tools for treatment of relapsed leukemia following HLA-mismatched stem cell transplantation. Mutis T (Reprint); Blokland E; Schrama E; **Goulmy E**. BONE MARROW TRANSPLANTATION (MAR 2001) Vol. 27, Supp. [1], pp. S1-S1. Publisher: NATURE PUBLISHING GROUP. HOUNDMILLS, BASINGSTOKE RG21 6XS, HAMPSHIRE, ENGLAND. ISSN: 0268-3369. Language: English.

L16 ANSWER 6 OF 36 SCISEARCH COPYRIGHT 2001 ISI (R)
2001:76905 The Genuine Article (R) Number: 372WB. Efficient in vitro induction of **minor histocompatibility antigen HA-1** specific cytotoxic T-lymphocytes using dendritic cells retrovirally transduced with **HA-1** coding gene segment.. Mutis T (Reprint); Wilke M; Ghoreschi K; Schrama E; Kamp J; Heemskerk M; Falkenburg J H F; **Goulmy E**. Leiden Univ, Med Ctr, Dept Immunohematol & Blood Transfus, Leiden, Netherlands; Univ Munich, Dept Dermatol, D-8000 Munich, Germany; Leiden Univ, Med Ctr, Dept Hematol, Leiden, Netherlands. BLOOD (16 NOV 2000) Vol. 96, No. 11, Part 1, pp. 582A-+. MA 2498. Publisher: AMER SOC HEMATOLOGY. 1900 M STREET. NW SUITE 200, WASHINGTON, DC 20036 USA. ISSN: 0006-4971. Pub. country: Netherlands; Germany. Language: English.

L16 ANSWER 7 OF 36 BIOSIS COPYRIGHT 2001 BIOSIS
2001:312013 Document No.: PREV200100312013. Efficient in vitro induction of **minor histocompatibility antigen HA-1** specific cytotoxic T-lymphocytes using dendritic cells retrovirally transduced with **HA-1** coding gene segment. Mutis, Tuna (1); Wilke, Martina (1); Ghoreschi, Kamran; Schrama, Ellen (1); Kamp, Janine (1); Heemskerk, Mirjam; Falkenburg, J. H. Frederik; **Goulmy, Els (1)**. (1) Dept. of Immunohematology and Blood Transfusion, Leiden University Medical Center, Leiden Netherlands. Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 582a. print. Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of

AB The **minor histocompatibility antigen** (mHag) **HA-1** is a hematopoietic system specific polymorphic antigen that can be recognized by cytotoxic T cells (CTLs) in the context of HLA-A2. **HA-1** specific CTLs exhibit strong anti-leukemia reactivity by lysing **HA-1** positive leukemic cells and their clonogenic precursors without affecting non-hematopoietic cells. Adoptive transfer of in vitro generated **HA-1** specific CTLs into **HA-1** positive patients with relapsed leukemia may therefore be curative with a low risk of graft versus host disease (GvHD). We have recently shown the feasibility of in vitro generation of **HA-1** specific CTLs from **HA-1** negative individuals using dendritic cells (DCs) pulsed with synthetic **HA-1** peptide. However, under GMP conditions, **HA-1** CTLs can not be generated from some donors using peptide pulsed DCs. We therefore investigated whether generation of **HA-1** specific CTLs is more effective using DCs that are retrovirally transduced to express the **HA-1** antigen. The 312 base pair gene segment coding for the **HA-1** CTL epitope was cloned into the retroviral vector LZRS. This vector was transduced into several cell lines including CD34+ DC progenitors with 10-40% efficiency. All retrovirally transduced cells showed stable and functional expression of the **HA-1** CTL epitope. CD34+ DC progenitors differentiated normally into immature DCs within 10-12 days and induced strong in vitro **HA-1** specific CTL responses in four out of six **HA-1** negative healthy unprimed individuals. The CTL lines contained 6-10% **HA-1** specific CTLs as determined by HLA-A2/**HA-1** peptide tetramers. The induction of **HA-1** specific CTLs by retrovirally transduced DCs required only one or two rounds of restimulation whereas CTL induction by peptide pulsed DCs required three to five rounds of restimulations. During the CTL induction, the retrovirally transduced DCs were detected at least seven days in the cultures and retained their immature phenotype. Our results demonstrate that retrovirally transduced immature DCs effectively induce **HA-1** specific CTL responses through their continuous presentation of the **HA-1** T cell epitope to unprimed T cell precursors.

L16 ANSWER 8 OF 36 SCISEARCH COPYRIGHT 2001 ISI (R)
2001:76463 The Genuine Article (R) Number: 372WB. Emergence of hematopoiesis-specific **minor histocompatibility antigen** (mHag) **HA-1** and HA-2 specific CD8+T cells associated with complete molecular remission after donor lymphocyte infusion (DLI) for relapsed CML.. Marijt W A F (Reprint); Kester M G D; **Goulmy E**; Mutis T; Drijfhout J W; Willemze R; Falkenburg J H F. Leiden Univ, Med Ctr, Dept Hematol, Leiden, Netherlands; Leiden Univ, Med Ctr, Dept Immunohematol, Leiden, Netherlands. BLOOD (16 NOV 2000) Vol. 96, No. 11, Part 1, pp. 478A-478A. MA 2055. Publisher: AMER SOC HEMATOLOGY. 1900 M STREET. NW SUITE 200, WASHINGTON, DC 20036 USA. ISSN: 0006-4971. Pub. country: Netherlands. Language: English.

L16 ANSWER 9 OF 36 CAPLUS COPYRIGHT 2001 ACS
1999:96392 Document No. 130:181466 Method for typing of **minor histocompatibility antigen HA-1**.
Goulmy, Els (Rijksuniversiteit Leiden, Neth.). PCT Int. Appl. WO 9905313 A2 19990204, 59 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,

FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-EP4928 19980723.

AB The present invention provides a method for typing of alleles of the **minor histocompatibility antigen HA-1** in a sample, with said method comprising: (a) contacting the genomic polynucleic acids in the sample with at least one pair of primers, whereby the 5'- and/or the 3'-primer of said at least one pair of primers specifically hybridize to target regions comprising polymorphic nucleotides in said alleles, and performing an amplification reaction; (b) for each of said at least one pair of primers detecting whether or not in step (a) an amplification product is formed; (c) inferring from the result of step (b) which **HA-1** allele is present in said sample. The present invention also provides a method for genomic typing of alleles of the **minor histocompatibility antigen HA-1** in a sample, with said method comprising: (a) amplifying a fragment of said alleles, with said fragment comprising at least one polymorphic nucleotide, by use of at least one pair of primers specifically hybridizing to conserved target regions in said alleles; (b) hybridizing the amplified product of step (a) to at least one probe specifically hybridizing to a target region comprising one or more polymorphic nucleotides in said allele; (c) inferring from the result of step (b) which **HA-1** allele is present in said sample. In addn., the present invention provides primers and probes for use in the above-mentioned methods. Diagnostic kits enabling said methods are also provided. The areas the invention is concerned with are bone marrow transplant, graft vs. host disease, severe aplastic anemia, leukemia and immune deficiency diseases.

L16 ANSWER 10 OF 36 CAPLUS COPYRIGHT 2001 ACS

1999:96271 Document No. 130:167164 The **HA-1** antigen.

Goulmy, Elsa Afra Julia Maria; Hunt, Donald F.; Engelhard, Victor H. (Rijksuniversiteit te Leiden, Neth.). PCT Int. Appl. WO 9905174 A1 19990204, 47 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-NL425 19980723.

AB The present invention discloses the peptide sequence of a so called minor H antigen. The minor H antigens are assocd. with the graft vs. host disease. The peptide and its derivs. find many uses in bone marrow transplantation, organ transplantation and in the treatment of leukemia. The peptide and its derivs. can be incorporated in vaccines, in pharmaceutical formulations and they can be used in diagnostic test kits. The peptide is derived from the **HA-1** minor antigen and has the sequence VLXDDLLEA, wherein X represents a histidine or an arginine residue. Both donors and recipients in bone marrow transplantation can be treated with the peptides, optionally in combination with other peptides, coupled to carriers, with suitable excipients and/or adjuvants.

L16 ANSWER 11 OF 36 CAPLUS COPYRIGHT 2001 ACS

1999:96270 Document No. 130:167163 The **HA-1** antigen.

Goulmy, Elsa Afra Julia Maria; Hunt, Donald Frederick; Engelhard, Victor Henry (Rijksuniversiteit te Leiden, Neth.). PCT Int. Appl. WO 9905173 A1 19990204, 57 pp. DESIGNATED STATES: W: AL, AM,

LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-NL424 19980723.

AB The present invention discloses the peptide sequence of a so-called minor H antigen. The minor H antigens are assocd. with the graft vs. host disease. The peptide and its derivs. find many uses in bone marrow transplantation, organ transplantation and in the treatment of leukemia. The peptide and its derivs. can be incorporated in vaccines, in pharmaceutical formulations and they can be used in diagnostic test kits. The peptide is derived from the **HA-1** minor antigen and has the sequence VLXDDLLEA, wherein X represents a histidine or an arginine residue. Both donors and recipients in bone marrow transplantation can be treated with the peptides, optionally in combination with other peptides, coupled to carriers, with suitable excipients and/or adjuvants.

L16 ANSWER 12 OF 36 SCISEARCH COPYRIGHT 2001 ISI (R)

1999:961963 The Genuine Article (R) Number: 263TD. Induction of **minor histocompatibility antigen HA-1** -specific cytotoxic T cells for the treatment of leukemia after allogeneic stem cell transplantation - Response. Mutis T (Reprint); **Goulmy E** . LEIDEN UNIV, MED CTR, DEPT IMMUNOHEMATOL & BLOOD BANK, LEIDEN, NETHERLANDS (Reprint). BLOOD (15 DEC 1999) Vol. 94, No. 12, pp. 4376-4376.

Publisher: W B SAUNDERS CO. INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399. ISSN: 0006-4971. Pub. country: NETHERLANDS. Language: English.

L16 ANSWER 13 OF 36 CAPLUS COPYRIGHT 2001 ACS

1999:797062 Document No. 132:92049 Induction of **minor histocompatibility antigen HA-1** -specific cytotoxic T cells for the treatment of leukemia after allogeneic stem cell transplantation. Reply to comments. Mutis, T.; **Goulmy, E.** (Department of Immunohematology and Blood Bank, Leiden University Medical Center, Leiden, Neth.). Blood, 94(12), 4376 (English) 1999. CODEN: BLOOAW. ISSN: 0006-4971. Publisher: W. B. Saunders Co..

AB A polemic in response to P. Brossart et al. (ibid, 4374) on evidence that HA-1H peptide-specific cytotoxic T-cells (CTL) induced in vitro using HA-1H peptide-pulsed monocyte-derived dendritic cells as APC from unprimed **HA-1**-neg. healthy donors are not only able to lyse primary leukemic blasts or immortalized B cells naturally expressing the HA-1H/H phenotype but also recognize heterozygous leukemic cells with the HA-1H/R phenotype, showing that these **HA-1**-specific CTL are of high affinity to the peptide/MHC complex.

L16 ANSWER 14 OF 36 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

1999432018 EMBASE Induction of **minor histocompatibility antigen HA-1**-specific cytotoxic T cells for the treatment of leukemia after allogeneic stem cell transplantation (multiple letters). Brossart P.; Spahlinger B.; Grunebach F.; Stuhler G.; Reichardt V.L.; Kanz L.; Brugger W.; Mutis T.; **Goulmy E.**. P. Brossart, Department of Hematology, University of Tubingen, Tubingen, Germany. Blood 94/12 (4374-4376) 1999.

Refs: 6.

ISSN: 0006-4971. CODEN: BLOOAW. Pub. Country: United States. Language: English.

of
immunotherapy of relapsed leukemia with ex vivo-generated cytotoxic T lymphocytes specific for hematopoietic system-restricted **minor histocompatibility antigens**. Mutis T; Verdijk R; Schrama E; Esendam B; Brand A; **Goulmy E**. (Department of Immunohematology and Blood Bank, Leiden University Medical Center, Leiden, The Netherlands.. Mutis@rullf2.leidenuniv.nl) . BLOOD, (1999 Apr 1) 93 (7) 2336-41. Journal code: A8G; 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB Allogeneic bone marrow transplantation (BMT) is a common treatment of hematologic malignancies. Recurrence of the underlying malignancy is a major cause of treatment failure. Donor-derived cytotoxic T lymphocytes (CTLs) specific for patients' **minor histocompatibility antigens** (mHags) play an important role in both graft-versus-host disease (GVHD) and graft-versus-leukemia (GVL) reactivities. mHags **HA-1** and HA-2 induce HLA-A*0201-restricted CTLs in vivo and are exclusively expressed on hematopoietic cells, including leukemic cells and leukemic precursors, but not on fibroblasts, keratinocytes, or liver cells. The chemical nature of the mHags **HA-1** and HA-2 is known. We investigated the feasibility of ex vivo generation of mHag **HA-1**- and HA-2-specific CTLs from unprimed mHag **HA-1**- and/or HA-2-negative healthy blood donors. **HA-1** and HA-2 synthetic peptide-pulsed dendritic cells (DCs) were used as antigen-presenting cells (APC) to stimulate autologous unprimed CD8(+) T cells. The ex vivo-generated **HA-1**- and HA-2-specific CTLs efficiently lyse leukemic cells derived from acute myeloid leukemia (AML) and acute lymphoid leukemia (ALL) patients. No lytic reactivity was detected against nonhematopoietic cells. Sufficient numbers of the CTLs can be obtained for the adoptive immunotherapy purposes. In conclusion, we present a feasible, novel therapy for the treatment for relapsed leukemia after BMT with a low risk of GVHD.

L16 ANSWER 16 OF 36 MEDLINE

1999321256 Document Number: 99321256. PubMed ID: 10395333. Tetrameric HLA class I-**minor histocompatibility antigen** peptide complexes demonstrate **minor histocompatibility antigen**-specific cytotoxic T lymphocytes in patients with graft-versus-host disease. Mutis T; Gillespie G; Schrama E; Falkenburg J H; Moss P; **Goulmy E**. (The Department of Immunohematology and Blood Bank, Leiden University Medical Center, The Netherlands.. Mutis@rullf2.leidenuniv.nl) . NATURE MEDICINE, (1999 Jul) 5 (7) 839-42. Journal code: CG5; 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB Graft-versus-host disease (GvHD) is a chief complication of allogeneic bone marrow transplantation. In HLA-identical bone marrow transplantation, GvHD may be induced by disparities in **minor histocompatibility antigens** (mHags) between the donor and the recipient, with the antigen being present in the recipient and not in the donor. Cytotoxic T lymphocytes (CTLs) specific for mHags of the recipients can be isolated from the blood of recipients with severe GvHD (ref. 3). A retrospective study demonstrated an association between mismatch for mHags **HA-1**, -2, -4 and -5 and the occurrence of GvHD in adult recipients of bone marrow from HLA genotypically identical donors. Tetrameric HLA-peptide complexes have been used to visualize and quantitate antigen-specific CTLs in HIV-infected individuals and during Epstein-Barr virus and lymphocytic choriomeningitis virus infections. Here we show the direct ex vivo visualization of

of 17 **HA-1** or HY mismatched marrow recipients, **HA-1**- and HY-specific CTLs were detected as early as 14 days after bone marrow transplantation. The tetrameric complexes demonstrated a significant increase in **HA-1**- and HY-specific CTLs during acute and chronic GvHD, which decreased after successful GvHD treatment. HLA class I-mHag peptide tetramers may serve as clinical tools for the diagnosis and monitoring of GvHD patients.

L16 ANSWER 17 OF 36 MEDLINE
1999316287 Document Number: 99316287. PubMed ID: 10384099.
Polyriboinosinic polyribocytidylic acid (poly(I:C)) induces stable maturation of functionally active human dendritic cells. Verdijk R M; Mutis T; Esendam B; Kamp J; Melief C J; Brand A; **Goulmy E**. (Department of Immunohematology and Blood Bank, Leiden University Medical Center, Leiden, The Netherlands.. verdijk@rullf2.medfac.leidenuniv.nl) . JOURNAL OF IMMUNOLOGY, (1999 Jul 1) 163 (1) 57-61. Journal code: IFB; 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.
AB For vaccination strategies and adoptive immunotherapy purposes, immature dendritic cells (DC) can be generated from adherent monocytes using GM-CSF and IL-4. Presently, the only clinically applicable method to induce stable maturation of DC is the use of supernatants of activated monocytes (monocyte-conditioned medium (MCM)). MCM contains an undefined mixture of cytokines and is difficult to standardize. Here we report that stable maturation of DC can be simply induced by the addition of polyriboinosinic polyribocytidylic acid (poly(I:C)), a synthetic dsRNA clinically applied as an immunomodulator. Poly(I:C)-treated DC show a mature phenotype with high expression levels of HLA-DR, CD86, and the DC maturation marker CD83. This mature phenotype is retained for 48 h after cytokine withdrawal. In contrast to untreated DC, poly(I:C)-treated DC down-regulate pinocytosis, produce high levels of IL-12 and low levels of IL-10, induce strong T cell proliferation in a primary allo MLR, and effectively present peptide Ags to HLA class I-restricted CTL. In conclusion, we present a simple methodology for the preparation of clinically applicable mature DC.

L16 ANSWER 18 OF 36 BIOSIS COPYRIGHT 2001 BIOSIS
1999:371048 Document No.: PREV199900371048. Monitoring cytotoxic T lymphocytes specific for **minor histocompatibility antigens** after bone marrow transplantation using tetramers of HLA-class I-mHag peptide complexes. Mutis, Tuna (1); Gillespie, Geraldine; Schrama, Ellen (1); Falkenburg, J. H. Frederik; Moss, Paul; **Goulmy, Els (1)**. (1) Department of Immunohaematology and Blood Bank, University Medical Center, Leiden Netherlands. British Journal of Haematology, (April, 1999) Vol. 105, No. SUPPL. 1, pp. 32. Meeting Info.: Annual Scientific Meeting of the British Society for Haematology Brighton, England, UK April 12-15, 1999 British Society for Haematology. ISSN: 0007-1048. Language: English.

L16 ANSWER 19 OF 36 BIOSIS COPYRIGHT 2001 BIOSIS
1999:357328 Document No.: PREV199900357328. Genomic identification of the **minor histocompatibility antigen HA-1** locus by allele specific PCR. Wilke, M. (1); Pool, J. (1); den Haan, J. M. M. (1); **Goulmy, E. (1)**. (1) Department of Immunohematology and Bloodbank, Leiden University Medical Center, Leiden Netherlands. Human Immunology, (1999) Vol. 60, No. SUPPL. 1, pp. S4. Meeting Info.: 13th Conference of the European Federation for

L16 ANSWER 20 OF 36 MEDLINE
1998128035 Document Number: 98128035. PubMed ID: 9461441. The **minor histocompatibility antigen HA-1**: a diallelic gene with a single amino acid polymorphism. den Haan J M; Meadows L M; Wang W; Pool J; Blokland E; Bishop T L; Reinhardus C; Shabanowitz J; Offringa R; **Hunt D F; Engelhard V H; Goulmy E.** (Department of Immunohematology and Bloodbank, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands.) SCIENCE, (1998 Feb 13) 279 (5353) 1054-7. Journal code: UJ7; 0404511. ISSN: 0036-8075. Pub. country: United States. Language: English.

AB The **minor histocompatibility antigen** (mHag) **HA-1** is the only known mHag for which mismatching is correlated with the development of severe graft versus host disease (GvHD) after human leukocyte antigen-identical bone marrow transplantation. **HA-1** was found to be a nonapeptide derived from an allele of the KIAA0223 gene. The **HA-1**-negative allelic counterpart encoded by KIAA0223 had one amino acid difference from **HA-1**. Family analysis with **HA-1** allele-specific polymerase chain reaction showed an exact correlation between this allelic polymorphism and the **HA-1** phenotype. **HA-1** allele typing of donor and recipient should improve donor selection and allow the determination of bone marrow transplantation recipients with high risk for **HA-1**-induced GvHD development.

L16 ANSWER 21 OF 36 MEDLINE
1999013046 Document Number: 99013046. PubMed ID: 9798702. **HA-1** and the SMCY-derived peptide FIDSYICQV (H-Y) are immunodominant **minor histocompatibility antigens** after bone marrow transplantation. Rufer N; Wolpert E; Helg C; Tiercy J M; Gratwohl A; Chapuis B; Jeannet M; **Goulmy E;** Roosnek E. (Department of Internal Medicine, University Hospital, Geneva, Switzerland.) TRANSPLANTATION, (1998 Oct 15) 66 (7) 910-6. Journal code: WEJ; 0132144. ISSN: 0041-1337. Pub. country: United States. Language: English.

AB BACKGROUND: Allogeneic bone marrow donors can be incompatible at different levels. Even HLA-identical pairs will be still incompatible for numerous **minor histocompatibility antigens** (mHag). Nevertheless, some incompatibilities are found to be associated with an increased risk of graft-versus-host disease (GVHD), which could be related to the way the immune system recognizes these antigens. METHODS: We determined the specificity of cytotoxic T-cell clones isolated during acute GVHD or during bone marrow graft rejection in patients (n=14) transplanted with marrow from donors who were histoincompatible for different minor and/or major histocompatibility antigens. RESULTS: We found a clear hierarchy among the different types of histoincompatibilities. In three combinations mismatched for a class I allele, all 27 clones isolated during GVHD were specific for the incompatible HLA molecule. In the 11 class I-identical combinations, 14 different mHags were recognized. The mHag **HA-1**, known to have a significant impact on the development of GVHD, was recognized in the two **HA-1**-incompatible combinations. In one of these combinations, which was sex mismatched, all 56 clones analyzed were directed against **HA-1**, demonstrating the dominance of this mHag. In the four **HA-1**-compatible, sex-mismatched combinations, the anti-H-Y response was directed against one immunodominant epitope rather than against multiple Y-chromosome-encoded

presented by T2 cells. Moreover, all cytotoxic T lymphocytes tested (n=6) were specific for the SMCY-derived peptide FIDSYICQV, originally described as being the H-Y epitope recognized in the context of HLA-A*0201. CONCLUSIONS: Some histocompatibility antigens are recognized in an immunodominant fashion and will therefore be recognized in the majority of mismatched combinations. Only for such antigens, correlations between mismatches and the occurrence of GVHD or graft rejections will be found.

L16 ANSWER 22 OF 36 MEDLINE
1999036482 Document Number: 99036482. PubMed ID: 9820596. Genomic identification of the **minor histocompatibility antigen HA-1** locus by allele-specific PCR.
Wilke M; Pool J; den Haan J M; **Goulmy E**. (Department of Immunohematology and Bloodbank, Leiden University Medical Center, The Netherlands.. ihbsecr@euronet.nl) . TISSUE ANTIGENS, (1998 Oct) 52 (4) 312-7. Journal code: VSV; 0331072. ISSN: 0001-2815. Pub. country: Denmark. Language: English.
AB Graft-versus-host disease (GvHD) can be a major complication of allogeneic bone marrow transplantation even in recipients of HLA genotype-identical transplants. Disparities in **minor histocompatibility antigens** (mHags) between donor and recipient are a potential risk for the development of GvHD. A mismatch for the mHag **HA-1** can cause GvHD in adult recipients of allogeneic bone marrow from HLA-identical donors. The mHag **HA-1**, first identified by HLA-A*0201-restricted cytotoxic T cells (CTLs), was recently chemically characterized as a nonapeptide. On the cDNA level, the **HA-1** locus has two alleles, HA-1H and HA-1R, which differ in two nucleotides, resulting in a single amino acid substitution. Here we report on the genomic structure of the **HA-1** locus. Isolation and sequencing of cosmid DNA encoding the **HA-1** peptide sequence revealed that the **HA-1** alleles are encoded by two exons. Two different primer sets were designed, each consisting of allele-specific primers and a common primer, and both sets containing intronic sequences. We performed genomic DNA typing of three families consisting of 24 HLA-A*0201-positive individuals. The predicted allele-specific products correlated in all cases with the mHag classification by CTLs and by RT-PCR. We demonstrate for the first time the genomic identification of the mHag **HA-1** locus. Prospective genomic typing for the **HA-1** alleles will improve donor selection and identify HLA-A*0201-positive recipients with a high risk for **HA-1**-induced GvHD.

L16 ANSWER 23 OF 36 BIOSIS COPYRIGHT 2001 BIOSIS
1998:471164 Document No.: PREV199800471164. Higher risk of immunodominant incompatibility for **HA-1, minor histocompatibility antigen**. Maruya, E. (1); Saji, H. (1); Yokoyama, S. (1); Ito, K.; **Goulmy, E.**; Juji, T.. (1) Dep. Res., Kyoto Red Cross Blood Cent., Kyoto Japan. Human Immunology, (1998) Vol. 59, No. SUPPL. 1, pp. 95. Meeting Info.: 24th Annual Meeting of the American Society for Histocompatibility and Immunogenetics Vancouver, British Columbia, Canada October 10-15, 1998 American Society for Histocompatibility and Immunogenetics. ISSN: 0198-8859. Language: English.

L16 ANSWER 24 OF 36 CAPLUS COPYRIGHT 2001 ACS
2000:6100 Document No. 132:292279 Nature of the **minor**

Leiden, 2300 RC, Neth.). HLA: [Proc. Int. Histocompat. Workshop Conf.], 12th, Meeting Date 1996, Volume 2, 39-41. Editor(s): Charron, Dominique. EDK, Medical and Scientific International Publisher: Sevres, Fr. (English)
1997. CODEN: 68MRA5.
AB A review and discussion with 10 refs. The role of the **minor histocompatibility antigens** (mHag), esp. in human bone marrow transplants and rejection, are described. The male specific mHag H-Y and 5 non-sex-linked mHag (designated **HA-1** to HA-5) were studied at 3 levels, i.e., immunogenetics, immunogenicity and tissue distribution. The HA-2 amino acid sequence has been confirmed; the peptide most probably originates from a member of the non-filament-forming class I myosin family. Another mHag recently identified is the male-specific antigen H-Y; the H-Y antigen presented by HLA-B7 appears to be an 11-residue peptide derived from SMCY, an evolutionarily conserved protein encoded by the Y chromosome.; the Y gene possibly functions as a gene controlling spermatogenesis. It is concluded that the mHag are peptides from polymorphic self proteins, and that they are derived from evolutionarily-conserved genes with important biol. functions.

L16 ANSWER 25 OF 36 MEDLINE
97080610 Document Number: 97080610. PubMed ID: 8921955. Conservation of **minor histocompatibility antigens** between human and non-human primates. den Haan J M; Bontrop R E; Pool J; Sherman N; Blokland E; **Engelhard V H; Hunt D F; Goulmy E**. (Department of Immunohaematology and Bloodbank, Leiden University Hospital, The Netherlands.. haan.j@rulgca.leidenuniv.nl) . EUROPEAN JOURNAL OF IMMUNOLOGY, (1996 Nov) 26 (11) 2680-5. Journal code: EN5; 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.
AB It is well accepted that **minor histocompatibility antigens** (mHag) can function as transplantation barriers between HLA-matched individuals. Little is known about the molecular nature and evolutionary conservation of mHag. It is only very recently that the first human mHag were identified. The HLA-A2.1-restricted mHag HA-2 and the HLA-B7-restricted mHag H-Y appeared to be peptides derived from polymorphic self proteins. Here we show that the HLA-A2.1-restricted mHag **HA-1**, HA-2, and the H-Y peptides are conserved between man, chimpanzees and rhesus macaques. Human cytotoxic T cell clones specific for the HLA-A2.1-restricted mHag **HA-1**, HA-2, and H-Y recognized HLA-A2.1 gene-transfected chimpanzee and rhesus macaque cells. High-pressure liquid chromatography fractionation of HLA-A2.1-bound peptides isolated from the HLA-A2.1-transfected chimpanzee cells revealed that the chimpanzee **HA-1** and HA-2 co-eluted with the human **HA-1** and HA-2. Subsequent amino acid sequencing showed that the chimpanzee HA-2 peptide is identical to the human HA-2 peptide. Our functional and biochemical results demonstrate that mHag peptides are conserved for over 35 million years.

L16 ANSWER 26 OF 36 MEDLINE
96133739 Document Number: 96133739. PubMed ID: 8532022. Mismatches of **minor histocompatibility antigens** between HLA-identical donors and recipients and the development of graft-versus-host disease after bone marrow transplantation. **Goulmy E**; Schipper R; Pool J; Blokland E; Falkenburg J H; Vossen J; Grathwohl A; Vogelsang G B; van Houwelingen H C; van Rood J J. (Department

281-5. Journal code: NOW; 0255562. ISSN: 0028-4793. Pub. country: United States. Language: English.

AB BACKGROUND. Graft-versus-host disease (GVHD) can be a major complication of allogeneic bone marrow transplantation even when the donor and recipient are siblings and share identical major histocompatibility antigens. The explanation may be a mismatch of **minor histocompatibility antigens**. We previously characterized five **minor histocompatibility antigens**, **HA-1**, 2, 3, 4, and 5, that are recognized by T cells in association with the major histocompatibility antigens HLA-A1 an A2. METHODS. We collected peripheral-blood leukocytes from 148 bone marrow recipients and their sibling donors, who were genotypically HLA identical.

Fifty pairs were positive for HLA-A1, 117 were positive for HLA-A2, and 19 were positive for both. The pairs were typed with cytotoxic-T-cell clones specific for **minor histocompatibility antigens** **HA-1**, 2, 3, 4, and 5. RESULTS. Mismatches of HA-3 were equally distributed among recipients in whom GVHD developed and those in whom it did not. By contrast, a mismatch of only **HA-1** was significantly correlated with GVHD of grade II or higher (odds ratio, infinity; P = 0.02) in adults. One or more mismatches of **HA-1**, 2, 4, and 5 were also significantly associated with GVHD (odds ratio, infinity; P = 0.006) in adults. These associations were not observed in children. CONCLUSIONS. A mismatch of **minor histocompatibility antigen HA-1** can cause GVHD in adult recipients of allogeneic bone marrow from HLA-identical donors. Prospective **HA-1** typing may improve donor selection and identify recipients who are at high risk for GVHD.

L16 ANSWER 27 OF 36 MEDLINE

97000507 Document Number: 97000507. PubMed ID: 8843592. Functional expression of **minor histocompatibility antigens** on human peripheral blood dendritic cells and epidermal Langerhans cells. van Lochem E; van der Keur M; Mommaas A M; de Gast G C; **Goulmy E**. (Department of Immunohematology and Bloodbank, Leiden University Hospital, The Netherlands.) TRANSPLANT IMMUNOLOGY, (1996 Jun) 4 (2) 151-7. Journal code: B32; 9309923. ISSN: 0966-3274. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Adequate presentation and cell surface expression of foreign **minor histocompatibility antigens** (mHag) to allogeneic T cells can lead to graft versus-host disease (GvHD) after HLA matched bone marrow transplantation (BMT). Cells of the dendritic cell (DC) lineage, including epidermal Langerhans cells (LC), are the most potent inducers of primary alloreactive T cell responses in vivo and in vitro. To explore the possible role of peripheral blood DC and of skin derived LC in the induction of alloimmune responses against mHag, we analysed the functional expression of mHag on these professional antigen-presenting cells (APC). To this end, cytotoxic T cell (CTL) clones specific for mHag H-Y and **HA-1** to HA-4 were used to demonstrate the presence of these antigens on highly purified DC and LC. Our results demonstrate that, like other cells of the hematopoietic lineage, DC and LC express all the mHag tested for. The functional expression of mHag on these potent APC suggests their involvement in the induction of mHag specific GvH directed T cell responses after allogeneic BMT.

L16 ANSWER 28 OF 36 MEDLINE

minor histocompatibility antigen-specific HLA-A*0201-restricted cytotoxic T-cell clones. **Goulmy E**; Pool J; van den Elsen P J. (Department of Immunohaematology and Blood Bank, University Hospital Leiden, The Netherlands.) BLOOD, (1995 May 1) 85 (9) 2478-81. Journal code: A8G; 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB **Minor histocompatibility antigens** (mHags) are involved in the induction of graft-versus-host disease (GVHD) after HLA-identical bone marrow transplantation. Previously, we isolated a series of HLA-A*0201-restricted cytotoxic T-cell (CTL) clones specific for the same mHag **HA-1** from peripheral blood of three unrelated patients who were suffering from GVHD. We have now analyzed the composition of the T-cell receptor (TCR) V regions of 12 of these mHag **HA-1**-specific HLA-A*0201-restricted CTL clones by DNA sequencing of the alpha and beta chains. Of these 12 clones, derived from three unrelated individuals, five independent TCR alpha V- and beta V-region sequences were established. The TCR alpha chains were composed of varying TCR alpha V and TCR alpha J genes with no obvious similarities in structure in the N regions. However, the TCR beta chains all used the TCR beta V6S9 gene segment, and showed remarkable similarities within the N-D-N regions; ie, three independent beta-chain sequences (originating from donors Ha and Gy) shared a leucine/valine amino acid pair, whereas the other two (originating from donors Ha and Wi) shared a serine/threonine pair, all at positions 99 and 100 of the TCR beta V region. In conclusion, the TCR analysis of **HA-1** mHag-specific CTL clones has shown that the **HA-1** mHag/HLA-A*0201 complex selects for highly similar TCR beta V regions.

L16 ANSWER 29 OF 36 MEDLINE

95362850 Document Number: 95362850. PubMed ID: 7635982. Recognition of clonogenic leukemic cells, remission bone marrow and HLA-identical donor bone marrow by CD8+ or CD4+ **minor histocompatibility antigen**-specific cytotoxic T lymphocytes. Faber L M; van der Hoeven J; **Goulmy E**; Hooftman-den Otter A L; van Luxemburg-Heijs S A; Willemze R; Falkenburg J H. (Department of Hematology, University Medical Center, Leiden, The Netherlands.) JOURNAL OF CLINICAL INVESTIGATION, (1995 Aug) 96 (2) 877-83. Journal code: HS7; 7802877. ISSN: 0021-9738. Pub. country: United States. Language: English.

AB We investigated whether minor histocompatibility (mH) antigen-specific cytotoxic T lymphocytes (CTL) can discriminate between leukemic hematopoietic progenitor cells (leukemic-HPC) from AML or CML patients, the HPC from their remission bone marrow (remission-HPC), and normal HPC from their HLA-identical sibling bone marrow donor (donor-HPC). Specific lysis by CD8+ CTL clones was observed not only of the leukemic-HPC but also of the donor-HPC in 3/4 patient/donor combinations expressing mH antigen **HA-1**, 3/5 combinations expressing mH antigen HA-2, 2/3 combinations expressing mH antigen HA-3, and 2/2 combinations expressing mH antigen HY-A1. In four patient/donor combinations the recognition of the donor-HPC was clearly less than of the leukemic-HPC, indicating differential susceptibility to lysis by these mH CTL clones. In addition, differential recognition of leukemic-HPC and remission-HPC within seven patients was analyzed. In one patient expressing the HA-2 antigen on the leukemic cells the recognition of the remission-HPC was clearly less than of the leukemic-HPC. One CD4+ CTL clone showed specific lysis of the leukemic-HPC from an AML patient and a CML patient as well as of normal remission-HPC and donor-HPC. These results illustrate that in general CD8+ and CD4+ mH antigen specific CTL clones do not differentially

to
a differential GVL effect.

L16 ANSWER 30 OF 36 MEDLINE
94154267 Document Number: 94154267. PubMed ID: 8111046. Recognition of **minor histocompatibility antigens** on lymphocytic and myeloid leukemic cells by cytotoxic T-cell clones. van der Harst D; **Goulmy E**; Falkenburg J H; Kooij-Winkelaar Y M; van Luxemburg-Heijs S A; Goselink H M; Brand A. (Department of Immunohematology and Bloodbank, University Medical Center, Leiden, The Netherlands.) BLOOD, (1994 Feb 15) 83 (4) 1060-6. Journal code: A8G; 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.
AB Clinical studies indicated an enhanced antileukemic effect of allogeneic bone marrow transplantation (BMT), as compared with autologous BMT. After allogeneic HLA-identical BMT, donor-derived cytotoxic T lymphocytes (CTLs) directed at minor histocompatibility (mH) antigens on the recipients, tissues can be shown. To evaluate the antileukemic reactivity of mH antigen-specific CTLs, we analyzed the expression of mH antigens on circulating lymphocytic and myeloid leukemic cells. We show that the defined mH specificities **HA-1** through HA-5 and H-Y are present on leukemic cells, indicating that mH antigen-specific CTLs are capable of HLA class I-restricted antigen-specific lysis of leukemic cells. Compared with interleukin-2-stimulated normal lymphocytes, leukemic cells of lymphocytic origin are less susceptible to T-cell-mediated cytotoxicity by the HA-2 mH antigen-specific CTL and the anti-HLA-A2 CTL clone. A possible explanation for this phenomenon is impaired expression of the LFA-1 adhesion molecule. Our study suggests that mH antigen-specific HLA class I-restricted CD8+ CTLs may be involved in the graft-versus-leukemia reactivity after allogeneic BMT.

L16 ANSWER 31 OF 36 MEDLINE
94083660 Document Number: 94083660. PubMed ID: 8260714. **Minor histocompatibility antigens HA-1**-, -2-, and -4-, and HY-specific cytotoxic T-cell clones inhibit human hematopoietic progenitor cell growth by a mechanism that is dependent on direct cell-cell contact. Marijt W A; Veenhof W F; **Goulmy E**; Willemze R; van Rood J J; Falkenburg J H. (Department of Hematology, University Medical Center, Leiden, The Netherlands.) BLOOD, (1993 Dec 15) 82 (12) 3778-85. Journal code: A8G; 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.
AB HLA-identical bone marrow transplantation (BMT) may be complicated by graft-versus-host disease or graft rejection. Both complications are thought to be initiated by recognition of minor histocompatibility (mH) antigens by HLA-restricted mH-antigen-specific T lymphocytes. Using HLA-A2-restricted mH antigens **HA-1**-, -2-, and -4-, and HY-specific cytotoxic T lymphocyte (CTL) clones, we studied the recognition by these CTL clones of interleukin-2 (IL-2)-stimulated T cells (IL-2 blasts), BM mononuclear cells (BMMNCs), and hematopoietic progenitor cells (HPCs). We showed that, when IL-2 blasts from the BM donors who were investigated were recognized by the **HA-1**-, -2-, and -4-, and HY-specific CTL clones, their BMMNCs and HPCs were recognized as well by these CTL clones, resulting in antigen-specific growth inhibition of erythrocyte burst-forming units (BFU-E), colony-forming units-granulocyte (CFU-G), and CFU-macrophage (CFU-M). the HA-2-specific CTL clone, however, inhibited BFU-E and CFU-G growth from four donors to a

antigen-specific stimulated CTLs or by stimulated BMMNCs were responsible for suppression of HPC growth or whether this effect was caused by direct cell-cell contact between CTLs and HPCs. HPC growth inhibition was only observed after preincubation of BMMNCs and CTLs together for 4 hours before plating the cells in semisolid HPC culture medium. When no cell-cell contact was permitted before plating, neither antigen-stimulated CTL nor antigen-nonstimulated CTLs provoked HPC growth inhibition. Culturing BMMNCs in the presence of supernatants harvested after incubation of BMMNCs and CTL clones together for 4 or 72 hours did also not result in HPC growth inhibition. Both suppression of HPC growth and lysis of IL-2 blasts and BMMNCs in the 51Cr-release assay appeared to be dependent on direct cell-cell contact between target cells and CTLs and were not caused by the release of inhibitory cytokines into the culture medium by antigen-specific stimulated CTLs or by stimulated BMMNCs. Our results show that mH-antigen-specific CTLs can inhibit HPC growth by a direct cytolytic effect and may therefore be responsible for BM graft rejection after HLA-identical BMT.

L16 ANSWER 32 OF 36 MEDLINE
94131814 Document Number: 94131814. PubMed ID: 8300407. Multiple **minor histocompatibility antigen** disparities between a recipient and four HLA-identical potential sibling donors for bone marrow transplantation. Marijt E A; Veenhof W F; **Goulmy E**; Kluck P M; Brand A; Willemze R; van Rood J J; Falkenburg J H. (Department of Hematology, University Medical Center, Leiden, The Netherlands.) HUMAN IMMUNOLOGY, (1993 Aug) 37 (4) 221-8. Journal code: G9W; 8010936. ISSN: 0198-8859. Pub. country: United States. Language: English.

AB A patient with acute leukemia and her family including four HLA-identical siblings were analyzed to select a donor who was not only HLA- but also minor histocompatibility (mH) antigen compatible for allogeneic bone marrow transplantation (BMT). The HLA-A2 restricted mH antigen-specific **HA-1**, -2, -4, and -5 cytotoxic T-lymphocyte (CTL) clones were used to type the family members for expression of these mH antigens. The patient and one HLA-identical sibling were compatible for these mH antigens. This sibling was selected as the bone marrow donor. The patient engrafted promptly but developed acute and chronic graft-versus-host disease. To study the presence of other mH antigen disparities between recipient and donor, host-versus-graft CTL lines and clones were generated by stimulation of recipient peripheral blood lymphocytes (PBLs) with donor bone marrow cells, and graft-versus-host CTL lines were generated after BMT by stimulation of PBLs of donor origin with recipient bone marrow cells. These CTL lines were cytotoxic to cells from the bone marrow donor and from the recipient, respectively, and to cells from several other family members. T-cell lines, generated from the patient after BMT by stimulation of recipient-derived PBLs with donor bone marrow cells, exhibited no specific cytotoxicity to donor or recipient cells. Chimerism studies after BMT revealed that the PBLs and T-cell lines generated after BMT were of donor origin.(ABSTRACT TRUNCATED AT 250 WORDS)

L16 ANSWER 33 OF 36 MEDLINE
93246305 Document Number: 93246305. PubMed ID: 8482585. A genetic analysis of human **minor histocompatibility antigens** demonstrates Mendelian segregation independent of HLA. Schreuder G M; Pool J; Blokland E; van Els C; Bakker A; van Rood J J; **Goulmy E**. (Department of Immunohaematology, University Hospital Leiden, The Netherlands.) IMMUNOGENETICS, (1993) 38 (2) 98-105. Journal code: GI4; 0420404. ISSN: 0093-7711. Pub. country: United States. Language: English.

antigens 15, and
fact that mH antigens are recognized in the context of MHC molecules creates an additional complication for reliable segregation analysis. To gain insight into the mode of inheritance of the mH antigens, we relied upon a series of HLA-A2-restricted cytotoxic T-cell (CTL) clones specific for four mH antigens. To perform segregation analysis independent of HLA-A2, we transfected HLA-A2-negative cells with the HLA-A2 gene: this results in the cell surface expression of the HLA-A2 gene product and, if present, mH antigen recognition. The mode of inheritance of the HLA-A2-restricted mH antigens **HA-1**, -2, -4, and -5 was analyzed in 25 families whose members either naturally expressed HLA-A2 or
were experimentally rendered HLA-A2-positive. Analysis of distribution of the mH antigens in the parent population among the mating types, together with their inheritance patterns in the families, demonstrated that the four mH antigens behaved as Mendelian traits, whereby each can be considered a product of a gene with two alleles, one expressing and one not expressing the detected specificity. We also showed that the loci encoding the **HA-1** and HA-2 antigens are not closely linked to HLA (lod scores Z (0 = 0.05) <-4.0). Some indication was obtained that the HA-4- and HA-5-encoding loci may be closely linked to HLA. While we are aware of the limited results of this nonetheless comprehensive study, we feel the similarity in immunogenetic traits between human and mouse mH antigens is at least striking.

L16 ANSWER 34 OF 36 MEDLINE
92373026 Document Number: 92373026. PubMed ID: 1380540. Tissue distribution of human **minor histocompatibility antigens**. Ubiquitous versus restricted tissue distribution indicates heterogeneity among human cytotoxic T lymphocyte-defined non-MHC
antigens. de Bueger M; Bakker A; Van Rood J J; Van der Woude F; **Goulmy E**. (Department of Immunohaematology, University Hospital, Leiden, The Netherlands.) JOURNAL OF IMMUNOLOGY, (1992 Sep 1) 149 (5) 1788-94. Journal code: IFB; 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB We determined the tissue distribution of 7 human minor histocompatibility (H) Ag. Each of these Ag is defined by one or more MHC class I-restricted CTL clones, previously generated from PBL primed against minor H Ag by HLA-identical bone marrow transplantation (BMT). CTL-mediated lysis of tissue-derived cells and cultured cell lines was used as an in vitro assay
for minor H Ag expression of several human tissues. The Ag HA-3 (HLA-A1-restricted), HA-4 (HLA-A2 restricted), HA-6 and HA-7 (HLA-B7 restricted), and the male-specific Ag H-Y (HLA-A2 and B7 restricted) were found to be expressed on cells of all tissues tested. In contrast, the HLA-A2-restricted Ag **HA-1** and HA-2 were demonstrated on PHA-blasts, EBV-BLCL, purified T cells, B cells, monocytes, and immature thymocytes, but could not be demonstrated on skin-derived cultured fibroblasts, keratinocytes, melanocytes, cultured epithelial cells of kidney proximal tubili, and umbilical cord vein-derived endothelial cells. Incubation of the latter cell lines with rIFN-gamma, rTNF-alpha, and/or rIL-1 alpha, in concentrations shown to maximally increase their susceptibility to lysis by allo-MHC class I CTL, did not induce recognition by **HA-1**- and HA-2-specific CTL in vitro. These results indicate an ubiquitous tissue expression of the minor
H Ag HA-3, -4, -6, -7 and H-Y in contrast to a to the hemopoietic cell lineage-restricted expression for **HA-1** and HA-2. The heterogeneity in tissue expression of T cell-defined, class I-restricted non-MHC Ag implies that they might be derived from intracellular proteins with either an ubiquitous or a more specialized cell type-specific function.

L16 ANSWER 35 OF 36 EMBASE COPYRIGHT 2001 [illegible]
91212594 EMBASE Document No.: 1991212594. Growth inhibition of clonogenic leukemic precursor cells by **minor histocompatibility antigen**-specific cytotoxic T lymphocytes. Falkenburg J.H.F.; Goselink H.M.; Van der Harst D.; Van Luxemburg-Heijs S.A.P.; Kooy-Winkelaar Y.M.C.; Faber L.M.; De Kroon J.; Brand A.; Fibbe W.E.; Willemze R.; **Goulmy E.**. Department of Hematology, Building 1, University Medical Center, P.O. Box 9600,2300 RC Leiden, Netherlands. Journal of Experimental Medicine 174/1 (27-33) 1991. ISSN: 0022-1007. CODEN: JEMEAV. Pub. Country: United States. Language: English. Summary Language: English.

AB Minor histocompatibility (mH) antigens appear to play a major role in bone marrow transplantation (BMT) using HLA-identical donors. Previously, we reported the isolation of major histocompatibility complex (MHC)-restricted mH antigen-specific cytotoxic T lymphocytes (CTL) from patients with graft-vs.-host disease or rejection after HLA-identical BMT. We have demonstrated that mH antigens can be recognized on hematopoietic progenitor cells, and residual recipient CTL specific for mH antigens expressed on donor hematopoietic progenitor cells may be responsible for graft rejection in spite of intensive conditioning regimens in HLA-identical BMT. Here, we investigated whether mH antigen-specific CTL directed against the mH antigens **HA-1** to HA-5 and the male-specific antigen H-Y were capable of antigen-specific inhibition of in vitro growth of clonogenic leukemic precursor cells. We demonstrate that mH antigen-specific CTL against all mH antigens tested can lyse freshly obtained myeloid leukemic cells, that these mH antigen-specific CTL can inhibit their clonogenic leukemic growth in vitro, and that this recognition is MHC restricted. We illustrate that leukemic (precursor) cells can escape elimination by mH antigen-specific CTL by impaired expression of the relevant MHC restriction molecule. We suggest that mH antigen-specific MHC-restricted CTL may be involved in vivo in the graft-vs.-leukemia reactivity after BMT.

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89067836 Document Number: 89067836. PubMed ID: 3199071. Cellularly defined **minor histocompatibility antigens** are differentially expressed on human hematopoietic progenitor cells. Voogt P J; **Goulmy E**; Veenhof W F; Hamilton M; Fibbe W E; Van Rood J J; Falkenburg J H. (Department of Hematology, University Medical Center, Leiden, The Netherlands.) JOURNAL OF EXPERIMENTAL MEDICINE, (1988 Dec 1) 168 (6) 2337-47. Journal code: I2V; 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB Previously, five CTL lines directed against minor histocompatibility (mH) antigens designated **HA-1**-5 have been established from peripheral blood of patients after allogeneic bone marrow transplantation (BMT), and have been characterized using population and family studies. All cell lines showed specific HLA class I-restricted lysis of PHA-stimulated peripheral blood target cells from donors positive for the particular mH antigens. After 4 h of incubation of the mH antigen HA-3-specific CTL line with bone marrow cells from HA-3+ donors, complete class I-restricted inhibition of colony growth of the hematopoietic progenitor cells was observed even at low E/T ratios, indicating that the HA-3 antigen is strongly expressed on hematopoietic stem cells. Therefore, this antigen may be a target structure in the immune-mediated rejection of the hematopoietic graft in case of incompatibility for this determinant between donor and recipient in allogeneic BMT. In contrast, incubation of bone marrow cells with the antigen-specific anti-**HA-1**, -2, -4, and -5 CTL lines did not result in growth inhibition of the

and using a very high E/T ratio, prolo-
donors were killed to some extent by the anti-mH-specific CTL lines, although the growth inhibition observed was minor and variable. Our results show that mH antigens are differentially expressed on human hematopoietic progenitor cells. Therefore, only some of these antigens may be targets in immune-mediated rejection of the bone marrow graft.

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